UNIVERSIDADE FEDERAL DE PELOTAS
Faculdade de Veterinária
Programa de Pós-Graduação em Veterinária

Dissertação

Infecção pelo Vírus Respiratório Sincicial Bovino: identificação da nucleolina como potencial receptor celular

Lariane da Silva Barcelos

Pelotas, 2024

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Dissertação apresentada ao Programa de Pós-Graduação em Veterinária da Faculdade de Veterinária da Universidade Federal de Pelotas, como requisito parcial à obtenção do título de Mestre em Ciências (área de concentração: Saúde Única).

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Pelotas, 2024

Universidade Federal de Pelotas / Sistema de Bibliotecas
Catalogação da Publicação

B242i Barcelos, Lariane da Silva

Infecção pelo vírus respiratório sincicial bovino [recurso eletrônico] : identificação da nucleolina como potencial receptor celular / Lariane da Silva Barcelos ; Geferson Fischer, orientador ; Mayara Fernanda Maggioli, coorientadora. — Pelotas, 2024.
116 f. : il.

Dissertação (Mestrado) — Programa de Pós-Graduação em Veterinária, Faculdade de Veterinária, Universidade Federal de Pelotas, 2024.

1. Imunologia. 2. Bovinos. 3. Receptor celular. 4. Vias de sinalização intracelular. 5. Virologia básica. I. Fischer, Geferson, orient. II. Maggioli, Mayara Fernanda, coorient. III. Título.

CDD 636.208962

Elaborada por Ubirajara Buddin Cruz CRB: 10/901

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Data da Defesa: 26/03/2024

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A minha família, pelo apoio e incentivo incondicionais.

Agradecimentos

Essa etapa poderia facilmente ser a mais extensa desta dissertação, tamanha gratidão que sinto. Por esse motivo, serei sucinta, na medida do possível. Inicialmente, agradeço a Deus, pelo dom da vida e pelas inúmeras bênçãos, algumas das quais descreverei a seguir.

Agradeço ao meu orientador, Dr. Geferson Fischer, que me acolheu no mundo científico, sempre guiando meus passos com um cuidado paternal. Não há palavras para agradecer o que devo ao seu trabalho, que mudou minha vida.

Ao Laboratório de Virologia e Imunologia (LABVIR) da UFPEL, lugar que por muito tempo foi a minha segunda casa. A todos que fizeram e fazem do LABVIR um lugar especial, minha sincera gratidão. Além de todo crescimento pessoal e profissional que o LABVIR me proporcionou, foi nesse lugar que pude conhecer o meu melhor amigo e companheiro nesse imenso mundo, a quem dedico o parágrafo seguinte.

Matheus Iuri Fruhauf. Você tem o meu coração e todo o meu amor. Não há palavras em nenhuma língua que possam expressar minha gratidão e felicidade por ser a sua pessoa. E você, a minha. Nosso relacionamento suportou o desafio da distância por um longo ano e estou certa de que enfrentaremos os próximos desafios com a mesma força e união.

A minha grande amiga, Dra. Cristina Mendes Peter, que além de ter me recebido no LABVIR, me ajudou a alçar voos mais distantes. Agradeço, também, a minha co-orientadora no mestrado e, agora, orientadora no doutorado, Dra. Mayara Fernanda Maggioli, obrigada por acreditar no meu potencial e me incentivar diariamente. Sua gentileza e cordialidade são uma inspiração para mim.

Aos meus pais, Mara e Laurestino da Silva Barcelos, que fizeram de meus sonhos os seus, suportando comigo a saudade, na certeza de que todo sacrifício traz consigo a perspectiva de um futuro melhor. A minha irmã, Maiara Barcelos

Gowert, por ser meu alicerce e ponto de referência. Obrigada por dividir comigo os ônus e bônus de fazer parte da nossa família.

A todos que passaram pelo meu caminho nesses últimos dois anos, mas que não foram especialmente supracitados. Eu tenho imensa gratidão a todos os passos que dei ao longo desse caminho e a todos que encontrei enquanto, lentamente, segui em frente.

E por último, mas não menos importante, eu gostaria de agradecer a mim. Por acreditar nos meus sonhos e por entender que a única maneira de ter coragem, é sentindo medo. E ir mesmo assim.

O presente trabalho foi realizado com apoio da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Código de Financiamento 001.

“Portanto, não se preocupem com o amanhã, pois o amanhã trará suas próprias inquietações. Bastam para hoje os problemas deste dia.” – Mateus 6:34.

Resumo

BARCELOS, Lariane da Silva. **Infecção pelo Vírus Respiratório Sincicial Bovino: identificação da nucleolina como potencial receptor celular.** 2024. 116f. Dissertação (Mestrado em Ciências) - Programa de Pós-Graduação em Veterinária, Faculdade de Veterinária, Universidade Federal de Pelotas, Pelotas, 2024.

O Vírus Respiratório Sincicial Bovino (BRSV) é um importante patógeno respiratório, relevante para a indústria pecuária em todo o mundo. A doença causada por este agente é responsável por perdas econômicas devido à queda na produtividade, provocada pelos sinais clinicos e as altas taxas de morbidade, além de mortalidade, especialmente em animais jovens, e os custos relacionados à prevenção e tratamento. Apesar da disponibilidade de vacinas contra o agente, há dificuldade no estabelecimento de imunidade duradoura nos rebanhos. Apesar de sua relevância, muitos fatores relacionados ao BRSV seguem desconhecidos, entre eles, o seu receptor celular. Além disso, a literatura carece de revisões atualizadas, especialmente abrangendo os aspectos relacionados a imunologia na infecção pelo vírus bovino. O presente trabalho, composto por dois artigos, visa contribuir na construção e manutenção de literatura completa e atualizada a respeito da virologia e imunidade ao BRSV. O primeiro artigo, de revisão bibliográfica, descreve processos essenciais ligados à resposta imunológica à infecção pelo BRSV, tais como as vias de sinalização, fatores associados à patogenicidade e mecanismos de escape imune, que contribuem para a alta morbidade e as dificuldades em alcançar imunidade duradoura. No segundo artigo da presente dissertação, objetivou-se analisar o envolvimento da nucleolina (NCL), receptor celular do RSV, na infecção pelo BRSV em células primárias bovinas. Análises via imunofluorescência indicam modulação da NCL durante a infecção pelo vírus. A neutralização da NCL resultou em uma significativa redução na infecção viral, alcançando de 30 a 86% de redução com doses de 1 e 5μg/mL, respectivamente ($p<0.0001$). A inibição funcional da NCL pelo aptâmero AS1411 resultou em efeito ainda mais pronunciado, com até 99% de redução na infecção (20μM, $p<0.0001$) comparado ao grupo controle. Coletivamente, os resultados sugerem que a NCL possa estar envolvida nos primeiros estágios da infecção de células primárias bovinas pelo BRSV. O presente trabalho visa expandir o entendimento atual das interações entre o hospedeiro natural e o BRSV, identificando a NCL como potential receptor celular deste vírus.

Palavras-chave: imunologia; bovinos; receptor celular; vias de sinalização intracelular; virologia básica.

Abstract

BARCELOS, Lariane da Silva. **Bovine Respiratory Syncytial Virus infection: identification of nucleolin as a potential cellular receptor.** 2024. 116p. Dissertation (Master degree in Sciences) - Programa de Pós-Graduação em Veterinária, Faculdade de Veterinária, Universidade Federal de Pelotas, Pelotas, 2024.

Bovine Respiratory Syncytial Virus (BRSV) is an important respiratory pathogen, relevant to the livestock industry worldwide. The disease caused by this agent is responsible for economic losses due to the drop in productivity, caused by clinical signs and high rates of morbidity, as well as mortality, especially in young animals, and the costs related to prevention and treatment. Despite the availability of vaccines against the agent, there is difficulty in establishing lasting immunity in herds. Despite its relevance, many factors related to BRSV remain unknown, including its cellular receptor. Furthermore, the literature lacks updated reviews, especially covering aspects related to immunology in bovine virus infection. The present work, composed of two papers, aims to contribute to the construction and maintenance of complete and updated literature regarding virology and immunity to BRSV. The first paper, a bibliographic review, describes essential processes linked to the immunological response to BRSV infection, such as signaling pathways, factors associated with pathogenicity, and immune escape mechanisms, which contribute to the high morbidity and difficulties in achieving lasting immunity. The second paper of this dissertation aimed to analyze the involvement of nucleolin (NCL), the RSV cellular receptor, in BRSV infection in bovine primary cells. Immunofluorescence analyses indicate a modulation of NCL expression during infection by the virus. Neutralization of NCL resulted in a significant reduction in viral infection, reaching 30 to 86% reduction with doses of 1 and 5μg/mL, respectively ($p<0.0001$). Functional inhibition of NCL by the AS1411 aptamer resulted in an even more pronounced effect, with up to a 99% reduction in infection (20μM, $p<0.0001$) compared to the control group. Collectively, these results suggest that NCL might be involved in the early stages of BRSV infection in bovine primary cells. This work aims to expand the current understanding of the interactions between the natural host and BRSV, identifying NCL as a potential cellular receptor for this virus.

Keywords: immunology; cattle; cell receptor; intracellular signaling pathways; basic virology.

Lista de Figuras

Lista de Tabelas

Lista de Abreviaturas e Siglas

APC	Célula apresentadora de antígeno, do inglês *antigen-presenting cell*
BRD	Doença respiratória bovina, do inglês *bovine respiratory disease*
BRSV	Vírus respiratório sincicial bovino, do inglês *Bovine Respiratory Syncytial Vírus*
BSA	Albumina do soro bovino, do inglês *bovine serum albumin*
CARDIF	Adaptador CARD (domínio de recrutamento de ativação de caspase), indutor de interferon-beta, do inglês *caspase activation recruitment domain (CARD)-adaptor inducing Interferon-beta*
CCL	Ligante de quimiocina com motivo C-C, do inglês *C-C motif chemokine ligand*
COX	Ciclooxigenase, do inglês *cyclooxygenase*
CXCL	Ligante de quimiocina com motivo C-X-C, do inglês *C-X-C motif chemokine ligand*
DC	Célula dendrítica, do inglês *dendritic cell*
dMEM	Meio eagle modificado de dulbecco, do inglês *dulbecco's modified eagle medium*
DNA	Ácido desoxirribonucleico, do inglês *deoxyribonucleic acid*
dsRNA	Ácido ribonucleico (RNA) de fita dupla, do inglês *double-stranded ribonucleic acid*
EGFR	Receptor do fator de crescimento epidérmico, do inglês *epidermal growth factor receptor*
e.g.	Por exemplo, do latim *exempli gratia*
F	Proteína de fusão, do inglês *fusion protein*
FPI	Proteína de inibição de fusão, do inglês *fusion protein inhibitor*

G	Glicoproteína de ligação principal, do inglês *major attachment glycoprotein*
GAGs	Glicosaminoglicanos, do inglês *glycosaminoglycans*
HPIV-3	Virus parainfluenza humano tipo 3, do inglês *human parainfluenza virus type 3*
ICAM-1	Molécula de adesão intercelular-1, do inglês *intercellular adhesion molecule 1*
IFN	Interferon
Ig	Imunoglobulina, do inglês *immunoglobulin*
IGF1R	Receptor do fator de crescimento semelhante à insulina 1, do inglês *insulin-like growth factor 1 receptor*
IKKε	Subunidade epsilon da quinase inibidora do fator nuclear kappa B, do inglês *inhibitor of nuclear factor kappa B kinase subunit epsilon*
IL	Interleucina, do inglês *Interleukin*
IPS-1	Estimulador 1 do promotor interferon-beta, do inglês *interferon-beta promoter stimulator 1*
IRAK	Quinase associada ao receptor de interleucina 1, do inglês *interleukin 1 receptor-associated kinase*
IRF-3	Fator regulador de interferon-3, do inglês *interferon regulatory factor-3*
ISGs	Genes estimulados por interferon, do inglês *interferon-stimulated genes*
ISREs	Elementos de resposta estimulados por interferon, do inglês *interferon-stimulated response elements*
JAK/STAT	Janus quinase/transdutores de sinal e ativadores de transcrição, do inglês *janus kinase/signal transducers and activators of transcription*
KEGG	Enciclopédia Kyoto de genes e genomas, do inglês *Kyoto encyclopedia of genes and genomes*
L	Proteína polimerase grande, do inglês *large polymerase protein*
LRR	Repetições ricas em leucina, do inglês *leucine-rich repeats*
M	Proteína de matriz, do inglês *matrix protein*
MAMP	Padrão molecular associado a micróbios, do inglês *microbial-associated molecular pattern*

MAVS	Proteína de sinalização antiviral mitocondrial, do inglês *mitochondrial antiviral-signaling protein*
MCP-1	Proteína químioatraente de monócitos 1, do inglês *monocyte chemoattractant protein-1*
MDA	Anticorpos derivados maternalmente, do inglês *maternally derived antibodies*
MDA-5	Proteína 5 associada à diferenciação do melanoma, do inglês *melanoma differentiation-associated protein 5*
MHC	Complexo principal de histocompatibilidade, do inglês *major histocompatibility complex*
MOI	Multiplicidade de infecção, do ingles *multiplicity of infection*
MPO	Mieloperoxidase, do inglês myeloperoxidase
mRNA	Ácido ribonucleico (RNA) mensageiro, do inglês *messenger RNA*
MVA	Vírus Vaccínia Ankara Modificado, do ingles *modified vaccinia ankara virus*
MyD88	Resposta primária de diferenciação mieloide 88, do inglês *myeloid differentiation primary response 88*
N	Nucleoproteína, do inglês *nucleoprotein*
nAbs	Anticorpos neutralizantes, do ingles *neutralizing antibodies*
NAK	Quinase de ativação do NFκB, do inglês *NFκB-activating kinase*
NAP1	Proteína 1 associada a quinase de ativação do NFκB, do inglês *NFκB-activating kinase-associated protein 1*
NCL	Nucleolina, do inglês *nucleolin*
NEMO	Modulador essencial do fator nuclear kappa-B, do inglês *nuclear factor κappa-B-essential modulator*
NETs	Armadilhas extracelulares de neutrófilos, do inglês *neutrophil extracellular traps*
NFκB	Fator nuclear potenciador da cadeia leve κ de células B ativadas, do inglês *nuclear factor κappa-light-chain-enhancer of activated B cells*
NK	Células assassinas naturais, do inglês *natural-killer cells*
NLRP3	Domínio contendo pirina 3 da família NLR, do inglês *NLR family pyrin domain containing 3*

NOD2	Domínio de oligomerização de nucleotídeos 2, do inglês *nucleotide oligomerization domain 2*
NRL	Receptor semelhante ao domínio de oligomerização de nucleotídeos, do inglês *nucleotide oligomerization domain-like receptor*
NS	Não estrutural, do inglês *nonstructural*
NSAID	Anti-inflamatório não-esteroidal, do inglês *non-steroidal anti-inflammatory drugs*
ORF	Fase aberta de leitura, do inglês *open reading frames*
P	Fosfoproteína, do inglês *phosphoprotein*
PBMC	Células mononucleares de sangue periférico, do inglês *peripheral blood mononuclear cells*
PKCζ	Proteína quinase C zeta, do inglês *protein kinase C zeta*
PPRV	Vírus da peste dos pequenos ruminantes, do inglês *peste des petits ruminants virus*
PRR	Receptor de reconhecimento de padrões, do inglês *pattern recognition receptor*
RANTES	Expressa e presumidamente secretada por células T normais, regulada por ativação, do inglês *regulated upon activation, normal T cell expressed and presumably secreted*
RdRp	RNA polimerase dependente de RNA, do inglês *RNA-dependent RNA polymerase*
RIG-I	Gene induzível por ácido retinóico I, do inglês *retinoic acid-inducible gene I*
RIP1	Proteína 1 de interação com o receptor, do inglês *receptor interacting protein 1*
RHDV	Virus da doença hemorrágica de coelhos, do inglês *rabbit hemorrhagic disease virus*
RLR	Receptores semelhantes ao gene induzido por ácido retinóico I, do inglês *retinoic acid-inducible gene I (RIG-I)-like receptor*
RNA	Ácido ribonucleico, do inglês *ribonucleic acid*
ROS	Espécies reativas de oxigênio, do inglês *reactive oxygen species*
RSV	Vírus respiratório sincicial, do inglês *Respiratory Syncytial Virus*

SARS-Cov-2	Síndrome respiratória severa aguda por coronavirus 2, do inglês *Severe Acute Respiratory Syndrome Coronavirus-2*
SH	Pequena proteína pequena hidrofóbica, do inglês *small hydrophobic protein*
ssRNA-	RNA de fita simples e sentido negativo, do inglês *single-stranded negative-sense RNA*
TAK1	Quinase 1 ativada pelo fator de crescimento transformador beta, do inglês *transforming growth factor beta- activated kinase 1*
TBK-1	Quinase de ligação a TANK 1 do inglês *TANK-binding kinase 1*
TCR	Receptor de célula T, do inglês *T-cell receptor*
TGF-β	Fator transformador de crescimento beta, do inglês *transforming growth factor beta*
Th	Célula T auxiliar, do inglês *T helper cell*
TIR	Receptor semelhante a Toll/interleucina-1, do inglês *toll/interleukin-1 receptor-like*
TIRAP	Proteína adaptadora contendo domínio TIR, do inglês *TIR domain containing adaptor protein*
TLR	Receptor semelhante a Toll, do inglês *toll-like receptor*
TNF-α	Fator de necrose tumoral alpha, do inglês *tumor necrosis factor-alpha*
TRAM	Molécula adaptadora relacionada ao TRIF, do inglês *TRIF-related adaptor molecule*
TRAF	Fator associado ao receptor TNF-α, do inglês *TNF-α-receptor-associated factor*
TRIF	Adaptador contendo domínio TIR que induz interferon-beta, do inglês *TIR-domain-containing adapter-inducing interferon-beta*
US	Estados Unidos, do inglês *United States*
USA	Estados Unidos da América, do inglês *United States of America*
VISA	Adaptador de sinalização induzido por vírus, do inglês *virus-induced signaling adaptor*

Lista de Símbolos

°C	Grau Celsius
<	Menor
>	Maior
α	Alpha
β	Beta
γ	Gamma
δ	Delta
ζ	Zeta
κ	Kappa

Sumário

1 Introdução

O Vírus Respiratório Sincicial Bovino (BRSV), como é chamado o *Orthopneumovirus bovis*, é um vírus envelopado de genoma RNA fita-simples de sentido negativo (ssRNA-), pertencente à família *Pneumoviridae* (Rima et al., 2017). Anteriormente, o BRSV fazia parte da família *Paramyxoviridae*, até que, em 2015, foi criada a família *Pneumoviridae*. Em 2016, o BRSV foi renomeado como *Bovine orthopneumovirus* e, em 2022, como *Orthopneumovirus bovis* (ICTV, 2022). Aderiremos à terminologia histórica para manter consistência com a literatura atual, que manteve uso do termo BRSV. Esse vírus é um importante patógeno envolvido no complexo de Doença Respiratória Bovina (BRD, do inglês *Bovine Respiratory Disease*), um complexo multifatorial responsável por prejuízos na bovinocultura em todo o mundo, levando a reduções na conversão alimentar, nas taxas de crescimento e no desempenho produtivo do rebanho (Brodersen, 2010; USDA, 2013; WHO, 2014). Apesar da alta taxa de morbidade associada, especialmente ao BRSV, são relatados mais animais apresentando lesões pulmonares no abate em comparação ao número de casos clínicos de BRD identificados em rebanhos, indicando que as perdas provocadas pela enfermidade, já altas, podem estar sendo subestimadas (Timsit et al., 2016). Além disso, as doenças respiratórias são uma das principais causas do uso de antimicrobianos em bovinos, trazendo consequências não somente ao animal e ao produtor, mas também à saúde pública (Andreotti; Nicodemo, 2004; USDA, 2013; WHO, 2014).

Descrito pela primeira vez em 1970, na Europa, o BRSV rapidamente foi detectado em outros continentes, como na Ásia e América (Inaba et al., 1970; Paccaud; Jacquier, 1970; Rosenquist, 1974). No Brasil, o primeiro relato da identificação do BRSV ocorreu em 1993. É válido ressaltar, no entanto, que esse estudo foi realizado de forma retrospectiva, utilizando amostras de 1987 a 1990. Desta forma, o vírus já se fazia presente em território nacional (Gonçalves et al., 1993). Os sinais clínicos atribuídos a infecção por BRSV vão desde secreção nasal e aumento da frequência respiratória, a dispneia severa, pneumonia e enfisema (Baker et al.,

1997; Bryson et al., 1978). O BRSV se assemelha ao seu homólogo, o Virus Respiratório Sincicial Humano (RSV) tanto em fatores clínicos quanto epidemiológicos (Colosia et al., 2023; Jia et al., 2021). Em ambas as infecções, os hospedeiros mais jovens ou imunossuprimidos são os mais suscetíveis e cuja sintomatologia costuma ser mais grave (Van Der Poel et al., 1994), porém, a imunidade gerada é de curta duração, tornando reinfecções comuns mesmo em adultos (Larsen et al., 2000; Russell et al., 2017; Sacco et al., 2014).

O RSV é a causa mais comum para infecções do trato respiratório inferior em crianças, responsável por inúmeras hospitalizações e, estima-se, 160.000 mortes anualmente no mundo. A infecção por RSV é a segunda maior causa de falência durante a primeira infância (Lozano et al., 2012; Mazur et al., 2021; Nair et al., 2010). Apesar da extrema relevância do RSV, a primeira vacina de uso humano no mundo foi lançada apenas em 2023 (FDA, 2023), após muitos anos de embargo, causados pelos resultados negativos enfrentados no seu desenvolvimento na década de 1960 (Anderson; Graham, 2013; Kim et al., 1969). Dada a importância e complexidade no estudo dos RSV, historicamente, predominam os estudos focados no vírus humano. Por muito tempo, as características do BRSV foram extrapoladas de seu homólogo humano, porém, apesar as semelhanças, cada agente possui suas peculiaridades. Os vírus respiratórios sinciciais são agentes hospedeiro-específicos, cuja resposta imune depende não somente do vírus, mas também do ambiente imunológico do hospedeiro, humano ou bovino, que apresenta, por sua vez, propriedades distintas (Anderson; Graham, 2013; Collins; Karron, 2013; Tizard, 2011).

O genoma do BRSV, ssRNA-, é constituído por >15kb, que codificam 10 genes contendo duas fases abertas de leitura (ORFs, do inglês *Open Reading Frames*) sobrepostas, resultando na produção de 11 proteínas: duas não estruturais (NS1 e 2), nucleoproteína (N), fosfoproteína (P), proteínas de matriz 1 e 2 (M1 e 2) e as glicoproteínas de envelope: de ligação (G), de fusão (F) e pequena hidrofóbica (SH)(Yunus et al., 2001). A proteína F destaca-se por proporcionar tanto a ligação quanto a entrada do vírus na célula, visto que as proteínas G e SH não são necessárias para a infecção *in vitro* (Karger et al., 2001; Karron et al., 1997). Estudos descrevem a nucleolina como um dos receptores celulares utilizados pelo RSV, definido, entre outros métodos, a partir da sua co-localização com a proteína F na fase de adsorção viral (Tayyari et al., 2011). Além dos *Orthopneumovirus*, a nucleolina

(NCL) é o receptor ou co-receptor de outros agentes virais, tais como o Parainfluenza tipo 3 (HPIV-3), que afeta o pulmão humano (Bose et al., 2004). O BRSV e o BPIV-3 são vírus intimamente relacionados (Makoschey; Berge, 2021), membros da mesma ordem viral, Mononegavirales (ICTV, 2022) e envolvidos na BRD (Kirchhoff et al., 2014).

Após a publicação do estudo realizado por Tayyari et al. (2011), a nucleolina foi considerada o receptor do RSV. Dentre os co-receptores envolvidos na infecção pelos RSV, são citadas as lectinas do tipo C, a molécula intercelular de adesão 1 (ICAM-1), o receptor do fator de crescimento epidérmico (EGFR), o Receptor semelhante a Toll 4 (TLR-4) e o receptor do fator de crescimento semelhante à insulina 1 (IGF1R)(Behera et al., 2001; Currier et al., 2016; Ghildyal et al., 1999; Griffiths et al., 2020; Kurt-Jones et al., 2000; Marr; Turvey, 2012). Mais recentemente foi confirmada a atividade da nucleolina, como co-receptor celular para o RSV humano, sendo descrita inicialmente uma ligação entre a proteína F do vírus e o IGF1R. Essa ligação provoca uma sinalização intracelular que culmina com a translocação da nucleolina para a superfície da membrana celular, onde ocorre sua ligação com a proteína F do vírus (Griffiths et al., 2020).

A NCL também está envolvida na infecção por SARS-CoV-2, incitando o aumento na expressão da NCL, que se transloca e interage com a proteína do nucleocapsídeo do vírus (Merino et al., 2023). Na infecção pelo vírus da raiva, a fosfoproteína viral interage com a NCL durante a replicação (Oksayan et al., 2015). Além de contribuir em infecções virais, seja na adsorção, penetração ou replicação, mais recentemente, foi demonstrado que a NCL inibe a replicação do vírus Peste des Petits Ruminants (PPRV). A proteína do nucleocapsídeo do PPRV colocaliza-se com NCL e tem sua replicação melhorada quando a expressão de NCL é inibida por interferência de RNA (Dong et al., 2020). Em relação à entrada viral, a NCL também está envolvida na infecção pelo Vírus Da Doença Hemorrágica Do Coelho (RHDV), mediando a entrada viral através da endocitose dependente de clatrina e interação com a proteína do capsídeo do RHDV (Zhu et al., 2018). As proteínas envolvidas na replicação e capacidade de escape imune do BRSV são um potencial alvo para futuras pesquisas. Espera-se que o presente trabalho, por compilar tais informações, possa contribuir na construção do conhecimento necessario ao desenvolvimento de novas técnicas e produtos ligados a profilaxia, diagnostico e tratamento. Há uma ampla gama

de vacinas disponíveis contra o BRSV, no entanto, elas não proporcionam imunidade duradoura e a indústria pecuária ainda enfrenta prejuízos econômicos decorrentes da infecção por BRSV (Hägglund et al., 2022; Miles, 2009).

A literatura atual carece de estudos focados nas propriedades do BRSV, que descrevam os processos imunológicos envolvidos na infecção e vacinação contra o agente conhecidos até o momento. Visto isso, o presente trabalha visa, primeiramente, revisar fatores pertinentes à imunologia relacionada ao BRSV, tais como:

- Os principais Receptores de Reconhecimento de Padrões (PRRs, do inglês *Pattern Recognition Receptor*) envolvidos na resposta contra o BRSV, quais Padrões Moleculares Associados a Micróbios (MAMPs, do inglês *Microbial-Associated Molecular Patterns*) eles reconhecem, bem como a via de sinalização iniciada por esta interação e a resposta desencadeada;
- Os mecanismos de escape desenvolvidos pelo BRSV, que contribuem para sua persistência prolongada e eliminação tardia pelo hospedeiro, para o aumento da transmissão e o estabelecimento de sinais clínicos mais severos.

Visando contribuir com a literatura atual acerca do BRSV, além de compilar os mecanismos imunológicos associados a infecção, o presente trabalho, na forma de um segundo artigo, busca analisar o papel da nucleolina na infecção por BRSV.

2 Artigos

2.1 Artigo 1

Interactions Between Bovine Respiratory Syncytial Virus and Cattle: Aspects of Pathogenesis and Immunity

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Publicado na revista Viruses

viruses

MDPI

Review

Interactions Between Bovine Respiratory Syncytial Virus and Cattle: Insights into Pathogenesis and Immunity

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Abstract: Bovine respiratory syncytial virus (BRSV) is a major respiratory pathogen in cattle, relevant to industry worldwide. BRSV is most severe in young calves and is often associated with stressful management events. The disease is responsible for economic losses due to lower productivity, morbidity, mortality, prevention, and treatment costs. BRSV employs different host immunity escaping mechanisms that interfere with effective long-term memory responses to current vaccines and natural infections. As members of the same genus, bovine and human RSV share a high homology and similarities in their genome, transmission, clinical signs, and epidemiology. This overlap presents an opportunity for One Health approaches and translational studies, with dual benefits. This review describes BRSV immunity processes, such as the signaling pathways involved in BRSV infection, the evading mechanisms contributing to morbidity, and the difficulties in achieving long-lasting immunity.

Keywords: immunology; innate immunity; signaling pathways.

Citation: To be added by editorial staff during production.

Academic Editor: Firstname Lastname

Received: date
Revised: date
Accepted: date
Published: date

1. Introduction

The bovine respiratory syncytial virus (BRSV) belongs to the Pneumoviridae family in the Orthopneumovirus genus and Mononegavirales order, a group of large enveloped negative-sense RNA viruses (ssRNA-) [1,2]. Formerly, BRSV was classified as Paramyxoviridae, but in 2016, the family Pneumoviridae was created with BRSV belonging to the genus Orthopneumovirus within this family. BRSV was then renamed as Orthopneumovirus bovis in 2022 [2]. We will adhere to the historical terminology to maintain consistency with previous literature. First described in Europe [3], BRSV detection in the USA was reported in 1974 [4] and is a relevant respiratory pathogen in the US and worldwide [5–8], acting either as the sole agent involved in respiratory disease in young calves or involved in the bovine respiratory disease (BRD) in cattle. BRD is a common illness in young cattle and the most important infectious cause of economic burden to the feedlot industry. The disease is complex and multifactorial, involving a combination of factors such as viral and bacterial pathogens, stress factors (e.g., weaning, transportation, commingling of cattle from different sources), and environmental conditions (e.g., dust, temperature fluctuations). An initial viral pathogen increases the susceptibility of calves to secondary infections and allows colonization of the lower respiratory tract by bacteria [9–11]. Fatalities, reduced production, prevention, and treatment costs contribute to associated economic losses. Still, more animals displaying lung lesions at slaughter are reported compared to the number of clinical BRD cases identified in herds, indicating that losses might be underestimated [12]. Respiratory disease also leads to reduced feed

conversion, growth rate, and performance, and it is one of the leading causes of antimicrobial use in cattle, with consequences to the animal, public health, and the environment [13,14]. Young calves are the most susceptible, but the generated immunity is short-lived, and reinfections occur even in older animals, maintaining the virus circulation [15,16].

2. BRSV genome and structure

The BRSV genome consists of a single-stranded negative-sense of 15.1 kb RNA encoding ten genes containing two overlapping open reading frames (ORFs), resulting in the production of 11 different proteins (Fig. 1A). The genome sequence from the 3 prime to 5 prime end includes the two nonstructural (NS) genes (NS1 and NS2), followed by nucleoprotein (N), phosphoprotein (P), matrix protein (M), small hydrophobic protein (SH), fusion glycoprotein (F), major attachment glycoprotein (G), matrix 2 (M2), and large polymerase protein (L). The M2 gene encodes two separate proteins, M2-1 and M2-2, from overlapping ORFs (Fig. 1A) [17].

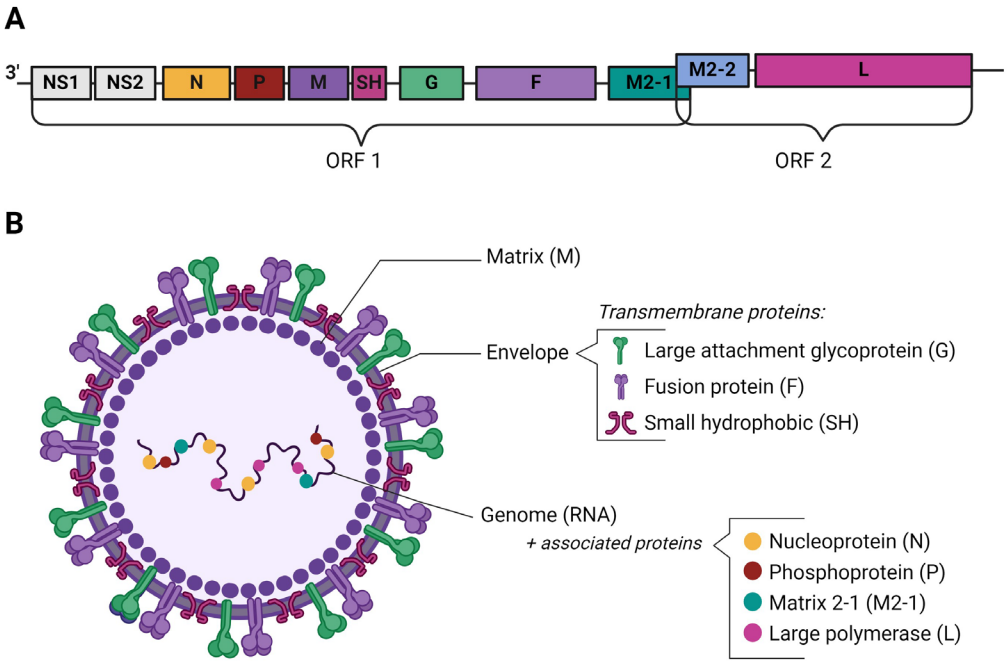

Figure 1. Schematic representation of BRSV genome organization and virion. (A) The BRSV genome organization is shown—the genome encodes 11 proteins from its ten genes. The M2 gene encodes the M2-1 and M2-2 proteins. (B) The circular morphology of the virion is shown. The attachment (G), fusion (F), and the small hydrophobic (SH) glycoproteins are embedded in the viral membrane. A matrix (M) protein layer lies underneath the viral membrane and gives the virion its overall scaffold and shape. The M2-1 protein interacts with the M and N proteins. The large polymerase subunit (L) and the phosphoprotein polymerase cofactor (P) are also associated with N and with the genome. Abbreviations: NS= Nonstructural proteins 1 and 2; N= Nucleocapsid; P= Phosphoprotein; M1= Matrix protein 1; SH= Small hydrophobic protein; G= Glycoprotein; F= Fusion protein; M2= Matrix protein 2; L= Large protein; ORF= Open reading frames 1 and 2. Figure created with BioRender.com.

Virions may be spherical but typically present as highly filamentous or pleomorphic structures measuring around 200 nm in diameter. The viral particles are encased in a lipid membrane about 7-15 nm thick, which is host derived. This membrane is adorned with cube-shaped projections forming well-defined bridges between virus particles, creating a unique network structure [18–20]. Three viral transmembrane surface glycoproteins are associated with the envelope: G, F, and the SH proteins, while M protein is located beneath the envelope's inner side (Fig. 1B). The lipid membrane encloses the nucleocapsid nucleoprotein core, with M protein forming an outer protein shell around the nucleocapsid [21]. The nucleocapsid is tightly associated with the single-stranded RNA and comprises four

viral proteins: N, P, the transcription processivity factor M2-1, and the large polymerase subunit [22,23]. The N protein is responsible for the structure that protects the genome (Fig. 1B), and the M2-1 and M2-2 proteins, along with the L protein, which acts as the RNA-dependent RNA polymerase (RdRp), are all involved in transcription and in the genome replication [22].

3. Viral Replication

Viral entry and replication are initiated by the interaction of the major attachment G protein to surface glycosaminoglycans (GAGs) on epithelial respiratory cells (Fig. 2A) [24,25], followed by the fusion to the host cell mediated by the F protein [22,26,27]. Alternatively, pneumoviruses fusion may require an internalization mechanism, such as micropinocytosis, clathrin- or caveolin-mediated endocytosis, with fusion taking place in an endosome upon proteolytic activation of the F protein (Fig. 2A) [26,28–30, and reviewed by 31]. Although G is the primary attachment protein, F protein also has attachment function, and its expression is sufficient to mediate infection in cell lines but results in an attenuated profile *in vivo* [32–34]. The fusion process is initiated when the F protein binds to a specific receptor on respiratory epithelial cells. This interaction triggers a conformational change in the F protein, converting it from its pre-fusion form to a post-fusion conformation, allowing the fusion peptide of the F protein to be inserted into the plasma membrane and a stable fusion pore formation [35]. As a result, the viral envelope and the host cell membrane merge, and the viral genome can enter the host cell (Fig. 2A) [35–37]. While studies confirming the cellular receptors for BRSV fusion are still lacking, human RSV F protein binds to nucleolin, which functions as a cell receptor for the virus [38], with several co-receptors also identified, including C-type lectins [39], toll-like receptor 4 (TLR-4) [40,41], intercellular adhesion molecule 1 (ICAM-1) [42], epidermal growth factor receptor (EGFR) [43], and insulin-like growth factor 1 receptor (IGF-1R) [44].

The viral RNA and associated nucleoproteins (N, P, and L) are released into the host cytoplasm upon fusion. Transcription takes place following a 3' to 5' gradient (Fig. 2A). The polymerase transcribes each gene resulting in sub-genomic mRNAs (5′ to 3′ orientation), which are in turn translated into viral proteins by the host cell machinery. The viral genome is replicated for progeny generation by translating the genome to antisense (5' to 3') by the polymerase, generating new negative-sense copies. Viral assembly and maturation occur at the plasma membrane [45,46]. Recent evidence shows that some initial steps of RSV virus assembly may alternatively happen within the cytoplasm before the complexes reach the plasma membrane [47,48]. Upon assembly, new virions bud out or stay closely associated with the host cell membrane (Fig. 2A) [22,49].

The F protein is primarily responsible for syncytium formation, the characteristic fusion of infected cells, from which BRSV derives its name [26]. While the binding of the virion to a host cell leads to viral entry [31,35,50], during viral replication, the F protein is expressed on the host cell plasma membrane mediating cell-to-cell fusion and multinucleated syncytium formation [51]. This cytopathic characteristic is a feature of infection and occurs both in cell lines (Fig. 2B) and *in vivo* (Fig. 2C). In infected animals, syncytia are observed mainly as large multinucleated cells formed by infected respiratory epithelial cells and are commonly found in lung tissues of affected animals (Fig. 2C and 2D). Syncytium formation may contribute to the pathogenesis of BRSV and is thought to influence viral replication kinetics and viral spread along neighboring cells while minimizing virus exposure to extracellular components of the immune system [33,52,53]. Additionally, due to its critical role in the viral infection process, the F protein is a target for vaccine development [54–57]. Vaccines that elicit a strong immune response against the F protein may protect cattle from BRSV infections. Still, strong antibodies directed against post-F conformation have been implicated in vaccine-enhanced disease with disastrous consequences in humans [58], with contradictory evidence in cattle [59,60]. Similarly, antiviral drugs that inhibit the function of the F protein could potentially prevent the virus from entering host cells, thereby blocking infection [61,62].

4. Common pathological findings

BRSV infection often triggers increased mucus production and inflammation, contributing to exudate accumulation in the bronchioles and alveoli. Bronchiolitis, characterized by inflammation, necrosis, and obstruction of the bronchioles, leads to airway constriction, impaired airflow, and respiratory distress, compromising the overall respiratory function (Fig. 2D). Lung consolidation ensues due to the accumulation of inflammatory cells, fluid, and debris in the alveoli and bronchioles, resulting in added respiratory distress and in the solid lung appearance in imaging studies or during macroscopic gross examination. Interstitial pneumonia, another common pathology finding, also occurs due to inflammation and thickening of the lung's interstitial tissue, worsening the respiratory distress. In severe cases, the virus can cause bronchiolar obstruction and alveolar damage, compromising the calf's overall respiratory function (Fig. 2D) [63–65].

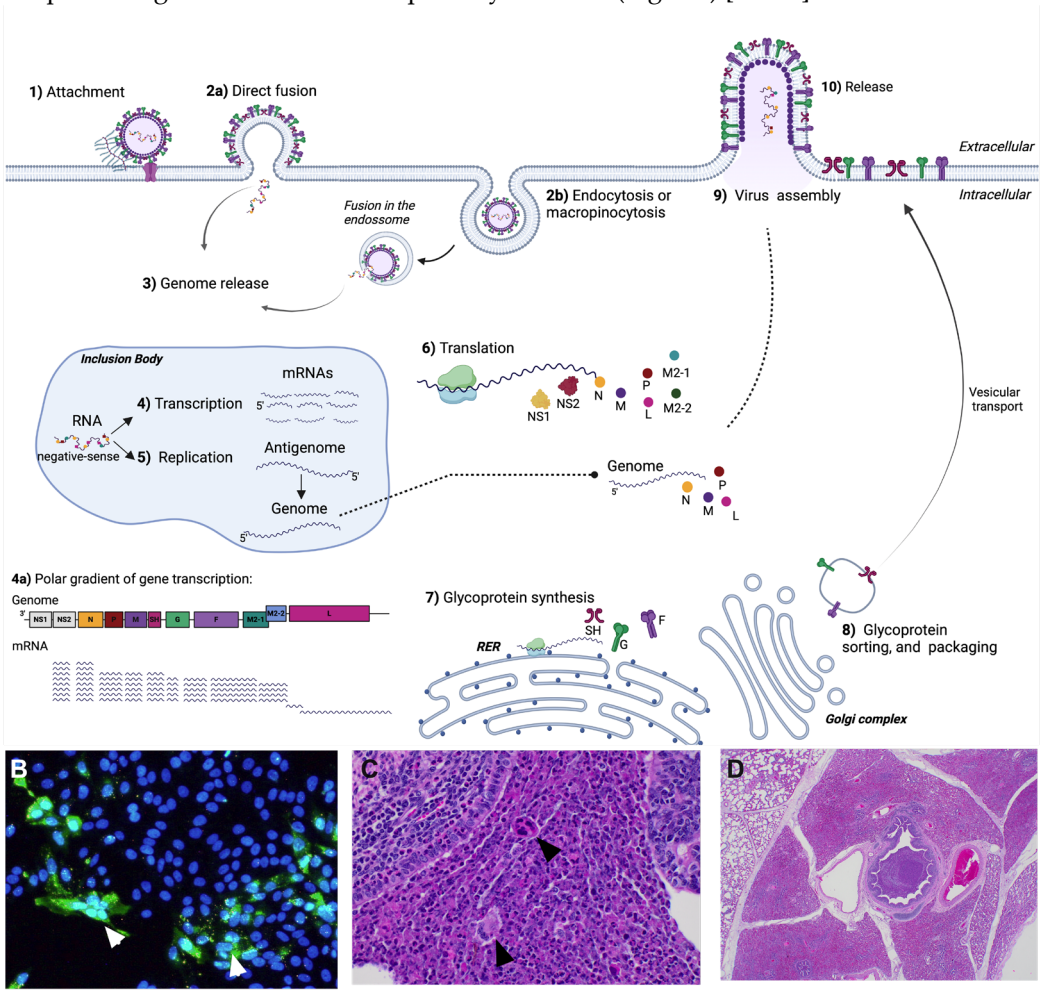

Figure 2. Schematic representation of BRSV replication, cytopathic effect in cell culture, and histological changes in an affected lung. **A)** Viral entry and replication cycle. **1)** Viral attachment and viral entry through **2a)** direct fusion to the host cell membrane mediated by F, or **2b)** virions may be internalized via micropinocytosis, clathrin- or caveolin-mediated endocytosis, with fusion taking place in an endosome. **3**) Upon fusion, the genome is released in the cytoplasm. **4)** Transcription of mRNAs. **4a**: Transcription occurs in an obligatorily sequential, polarized manner to generate 10 sub genomic mRNAs following a gradient in relation to the order in which the genes occur in the ssRNA (genes located closer to the 3' end of the ssRNA molecule are transcribed at higher levels than genes located towards the 5' end). **5)** The antigenome is replicated for progeny generation. **6)** mRNA from step **4** is translated into viral proteins, with the exception of G, F, and SH. **7)** Glycoproteins G, F, and SH are synthesized in the rough endoplasmic reticulum. **8)** Glycoproteins G, F, and SH undergo maturation, modification, and packaging in the Golgi complex and are transported in vesicles to the cell membrane. **9)** Viral assembly: The N protein binds to the newly synthesized viral RNA genome, forming a ribonucleoprotein (RNP) complex, which also includes other genome associated proteins (P, L, M2-1). The matrix (M) protein interacts with the RNP complex and assists its transport to the

plasma membrane, where assembly occurs. The M protein bridges the RNP complex with the inner surface of the cell membrane, where the G, F, and SH proteins are embedded. **10)** Newly formed particles bud off or stay associated to the host cell membrane. **B)** Immunofluorescence image depicting syncytia (white arrows) in bovine turbinate cells infected with BRSV (MOI: ~0.5, 48h post-infection). Green fluorescence represents BRSV-infected cells indicating viral presence. The blue fluorescence represents the cell nuclei stained with DAPI (4',6-diamidino-2-phenylindole). **C)** Syncytia in the lung of a calf infected with BRSV in paraffin-embedded lung tissue sections, photomicrograph showing bronchiolar epithelial cells forming multinucleated syncytia cells (black arrowheads); and **D)** Representative histological changes in the lungs of infected calves. A lower magnification image of the lung tissue depicted in C, showing interstitial thickening and wide interlobular septae, severe bronchointerstitial pneumonia with necrotizing bronchiolitis, and alveolar collapse. Note bronchioles are filled with neutrophils, sloughed epithelial cells, and necrotic cell debris. Tissue from a 12-week-old calf experimentally infected with BRSV (10 days post-infection, aerosol delivery ~10^5 TCID). Abbreviations: NS= Nonstructural proteins 1 and 2; N= Nucleocapsid; P= Phosphoprotein; M= Matrix protein; SH= Small hydrophobic protein; G= Glycoprotein; F= Fusion Protein; L= Large protein; mRNA= messenger RNA. Figure created with BioRender.com.

5. Host-pathogen interaction

Infection and replication are integral to the virus life cycle, but these processes expose viruses to detection and elimination by the host immune mechanisms. Viral nucleic acids, replication products, and some viral proteins are common detection targets of the innate immune system [66]. The timing and the kinetics of early viral detection by innate immune mechanisms significantly influence infection progression, the establishment of adaptive immunity, and ultimately impact disease outcome. Likewise, BRSV has evolved many escaping mechanisms to evade, delay, and/or subvert immune detection and antiviral host responses [67,68].

The host immune system is equipped with an arsenal of pattern recognition receptors (PRRs) that turn microbial and danger-sensing into immediate host defense responses (Table 1 and Fig. 3 and 4). Viral detection results in a series of signaling pathways that will culminate with the secretion of type I interferons (IFNs), pro-inflammatory cytokines, and other inflammatory mediators, resulting in leukocyte recruitment, tissue infiltration, and later on, T cell activation and antibody production. While these are steps necessary to achieve viral clearance, those responses frequently contribute to clinical signs, including fever, cough, increased mucus production, anorexia, respiratory distress, and depression. When host responses are dysregulated or poorly effective, they contribute to clinical disease, tissue damage, and pathology [69,70].

5.1. Innate Immunity

Initial BRSV infection and replication occur in the superficial layer of the nasal, tracheal, and bronchial epithelium, with later replication in the bronchiolar and alveolar epithelium. The host innate detection is based on the presence of PRRs, which detect distinct evolutionarily conserved structures on pathogens, termed microbial-associated molecular patterns (MAMPs). PRRs include the toll-like receptors (TLRs), the retinoic acid-inducible gene I-like receptors (RLRs), the nucleotide oligomerization domain-like receptors (NLRs), and cytosolic DNA sensors. PRRs are expressed in cells of the immune system as well as non-immune cells and are present in multiple cellular compartments (cytosol, endosomal, or cell membrane), allowing virally infected cells to trigger defense mechanisms that decrease replication, signal infection to neighboring cells, and to innate and adaptive immunity [71–73]. In response to viral MAMPs detection, cells produce type I IFNs, particularly IFN-α and IFN-β, which are crucial in inhibiting viral replication and spread. These IFNs induce an antiviral state in neighboring cells and activate the Janus kinase/signal transducers and activators of transcription (JAK-STAT) signaling pathways, leading to the expression of hundreds of IFN-stimulated genes with antiviral functions [74,75].

While some viral proteins can trigger PRRS, nucleic acids detected in intracellular spaces during replication are predominant viral molecular patterns. Upon viral entry into host target cells, the BRSV viral RNA and its replication products are recognized by

retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA-5), leading to the production of type I IFNs and establishing an antiviral state within the infected and neighboring cells. In this state, various defense mechanisms are upregulated, including the expression of antiviral proteins, to thwart viral replication and spread. This intricate interplay between cytosolic detection and the establishment of an antiviral state is a crucial aspect of the innate immune system's ability to combat viral infections effectively [75–77]. In addition to type I IFN, the innate immune cells release pro-inflammatory cytokines and mediators, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), which contribute to the inflammation and to the recruitment of immune cells to the site of infection, while also mediating systemic clinical signs associated with the infection.

While the nucleotide oligomerization domain 2 (NOD2) and RIG-I are the most important NLR and RLR involved in the immune response against BRSV, the heterodimer TLR-2-TLR-6, the TLR-3, 4, 7, and TLR-8 have been shown to recognize BRSV [16,73]. It is essential to highlight that the cellular expression of PRRs differs among different cell types (Table 1), as do the signaling molecules involved in the pathway that leads to cytokine and IFN production. For example, dendritic cells are specialized in expressing TLR-3, 7, and 9 with activation of interferon regulatory factor 7 (IRF7), leading to a strong type I IFN secretion; in contrast to macrophages, known for their high expression of TLR-2 and TLR-4, primarily producing pro-inflammatory cytokines [71,78]. In cattle, γδ T cells also express TLR-2, TLR-3, TLR-4, and TLR-7 [79–81]. Epithelial cells are crucial in the BRSV response, as they are not only a physical barrier but also the virus' main target and, therefore, involved in immune activation. BRSV G protein binds to sialic acid residues on cell surfaces, and the F protein works along with G to mediate cellular invasion [22]. This virus has been shown to infect different respiratory tract cells in the trachea, bronchiolar cells, and pneumocytes [72,82]. The main PRRs involved in the anti-BRSV response, cell types in which they are present, their location within the cell, and the MAMPs each one recognizes (their main ligands) are described in Table 1.

Table 1. Pattern recognition receptors involved in the immune response against bovine respiratory syncytial virus.

PRR	Cell types	Location	Ligand
TLR-2/6	Dendritic cells, monocytes, mast cells, eosinophils, basophils, epithelial cells	Cell surface	Large attachment Glycoprotein (G)
TLR-3	Dendritic cells, macrophages, mast cells, epithelial cells, γδ T cells	Endosome	Viral dsRNA
TLR-4	Dendritic cells, macrophages, mast cells, neutrophils, eosinophils, epithelial cells	Cell surface	Fusion protein (F)
TLR-7	Dendritic cells, macrophages, eosinophils, epithelial cells, γδ T cells	Endosome	Viral ssRNA
TLR-8	Dendritic cells, macrophages, neutrophils, monocytes, regulatory T cells, epithelial cells	Endosome	Viral ssRNA
NOD2	Dendritic cells, macrophages, monocytes, epithelial cells	Cytoplasm	Viral ssRNA

RIG-I	Dendritic cells, macrophages, neutrophils, epithelial cells	Cytoplasm	Viral ssRNA
MDA-5	Dendritic cells, macrophages, neutrophils, epithelial cells	Cytoplasm	Viral dsRNA

[49,83–88]. Abbreviations: PRR= Pattern recognition receptor; TLR= Toll-like receptor; NOD2= Nucleotide oligomerization domain 2; RIG-I= Retinoic acid-inducible gene 1; MDA-5= Melanoma differentiation-associated protein 5; ssRNA= single-stranded RNA; dsRNA= double-stranded RNA.

5.1.1. Pattern recognition receptors signaling pathways

NLRs and RLRs are key components of the cytosolic sensing system within cells. These receptors play a crucial role in the innate immune response, detecting MAMPs and damage-associated molecular patterns (DAMPs) within the cytosol of cells. NLRs and RLRs are involved in the immune response against BRSV (Fig. 3). The NOD2 cytosolic receptor detects viral ssRNA and associates to mitochondrial antiviral-signaling protein (MAVS), also known as IFN-β promoter stimulator 1 (IPS-1), virus-induced signaling adaptor (VISA) or caspase activation recruitment domain-adaptor inducing IFN-β (CARDIF) [73]. After interaction with MAVS, transcription factor interferon regulatory factor-3 (IRF3) and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) are activated and lead to type I IFNs and pro-inflammatory cytokines production, respectively [89].

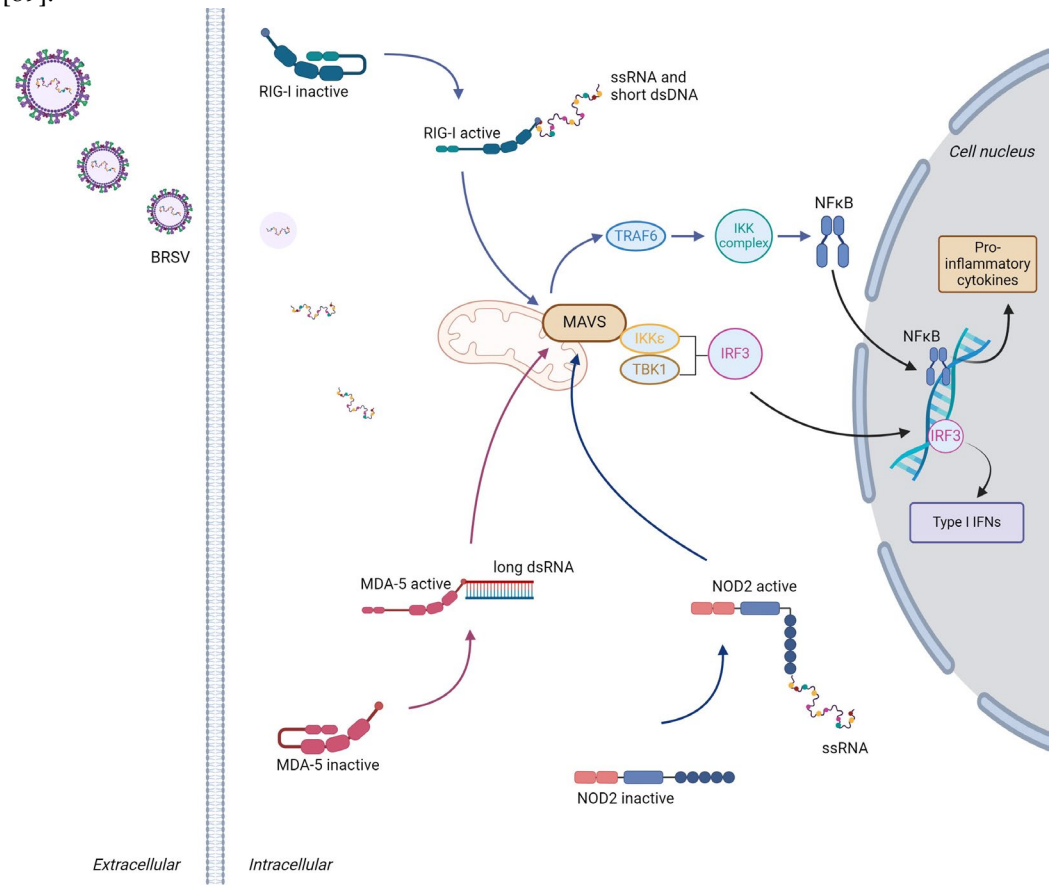

Figure 3. Schematic representation of RIG-I, MDA-5, and NOD2 signaling pathways. Abbreviations: BRSV= Bovine respiratory syncytial virus; ssRNA= single-stranded RNA; dsRNA= double-stranded RNA; TRAF6= Tumor necrosis factor-alpha (TNF-α)-receptor-associated factor 6; NFκB= Nuclear factor kappa B; MAVS= Mitochondrial antiviral-signaling protein; IKKε= Inhibitor of nuclear factor kappa-B kinase ε; TBK1= TANK binding kinase 1 (TBK1); IRF3= Interferon regulatory factor 3. Figure created with BioRender.com.

As for the other cytosolic detection, RIG-I is activated by 5′ triphosphorylated ends and dsRNA, whereas MDA-5 is activated by long dsRNA molecules independent of their 5′ phosphorylation status. RIG-I and MDA-5 have been shown to detect RSV, with some evidence in cattle (BRSV) [76,90]. RIG-I also uses MAVS as an intermediate, and the pathway culminates with IRF3 and NFκB activation and secretion of type I IFN and pro-inflammatory cytokines [87,91]. The RIG-I activity in RSV recognition was shown in cell lines and primary cell cultures [92–95], and *in vivo* in mice [96], human patients hospitalized due to RSV [97], and in BRSV infected calves [69,98,99].

The sensing of cytosolic dsRNA by MDA-5 also recruits the adaptor protein MAVS, leading to the activation of TANK-binding kinase 1 (TBK1) and the inhibitor of nuclear factor kappa-B kinase ε (IKKε) [100]. TBK1 and IKKε induce IRF3 phosphorylation, which culminates with its translocation to the nucleus, where IRF3 induces type I IFNs production [73]. According to Loo et al. [101], RIG-I, but not MDA-5, was crucial in the immune defense against RSV, and cells lacking RIG-I were more permissive to RSV infection than wild-type and MDA-5-lacking cells. MDA-5 may also be involved in the RSV modulation of type I IFN, as it colocalizes with the N protein inside inclusion bodies early post-infection [94].

TLRs are structurally constituted of leucine-rich repeats (LRRs), responsible for ligand recognition, and a toll/interleukin-1 receptor-like (TIR) domain. The TIR domain is responsible for interacting with adaptor proteins to engage the signaling process [102]. Generally, every TLR uses the myeloid differentiation primary response 88 (MyD88) signaling pathway, except for TLR-3, which uses only TIR-domain-containing adapter-inducing interferon-β (TRIF) as an adaptor protein, and TLR-4, which can use both MyD88 and TRIF [103].

TLR-2 forms a dimer with either TLR-1 or TLR-6; however, a previous study showed that especially the RSV species are recognized by the dimer TLR-2-TLR-6, and not TLR-2-TLR-1 [104]; and that RSV G protein is recognized by the TLR2-6 dimer [105]. The signaling pathway executed by TLR-2 uses TIRAP as the adaptor to MyD88, leading to the NFκB translocation and pro-inflammatory cytokines production [106]. The TLR-4 was the first TLR reported to recognize viral pathogens and bind to the F protein of RSV [40] and BRSV [107]. Also, TLR-4 polymorphism is related to human RSV disease severity [108]. TLR-4 pathway recruits either MyD88 or TRIF, and these pathways may be competitive (Fig. 4) [109]. TIRAP-MyD88 regulates early NFκB activation and production of pro-inflammatory cytokines, while the TRIF-dependent pathway involves the recruitment of the adaptor proteins TRIF and TRIF-related adaptor molecule (TRAM). TRAM-TRIF signals activate IRF3 via TRAF3. IRF3 activation induces the production of type I IFNs [110–112]. On the MyD88-dependent pathway, once the TLR-4 recognizes the BRSV F protein (Fig. 4A), the intracellular domain of the TLR recruits MyD88, which attracts the interleukin 1 Receptor (IL-1R)-associated kinase 1 (IRAK1) and 4 (IRAK4), forming a complex known as Myddosome [113]. This formation activates IRAK4, which phosphorylates IRAK1, subsequently releasing IRAK1, which associates itself to TNF-α-receptor-associated factor 6 (TRAF6), activating it. The activated TRAF6 forms a new complex, along with transforming growth factor beta (TGF-β)-activated kinase 1 (TAK1), that is now activated. TAK1 then activates the IKK complex, which is composed of IKKα, IKKβ, and IKKγ, also known as NFκB-essential modulator (NEMO). Once activated, the IKK complex phosphorylates the inhibitor of NFκB, which can now translocate to the cell nucleus, where it leads to the transcription of critical pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α [71,114,115].

The secondary route executed by TLR-4 uses TRIF (also known as TICAM-1) in place of MyD88 and leads to increased production of type I IFNs [103]. This MyD88-independent pathway is similar to the endosomal TLR-3 signaling, shown in Figure 4B. Upon TRIF adaptor protein recruitment, TRAF6 is engaged, which in turn interacts with both TRAF3 and receptor interacting protein 1 (RIP1). TRAF6 is involved in the NFκB activation by forming a complex with RIP1 and TAK1 that will activate the IKK complex, phosphorylating IKκA, which in turn phosphorylates the NFκB inhibitor nuclear factor of kappa

light polypeptide gene enhancer in B-cells inhibitor alpha (IκBα). Upon phosphorylation, IκBα dissociates from NFκB, undergoing ubiquitination and degradation. Once IκBα dissociates from the complex, NFκB can translocate to the nucleus, where it will induce the production of inflammatory cytokines (Fig. 4) [78,116,117]. Alternatively, TRIF recruits TRAF3, which binds to NFκB-activating kinase (NAK)-associated protein 1 (NAP1), attracting TANK Binding Kinase 1 (TBK1) and IKKε, forming a complex. TBK1 and IKKε are responsible for phosphorylating the IRF3. Phosphorylated IRF-3 forms dimers that are the active form of the transcription factor and translocate into the nucleus IRF3. Once in the nucleus, IRF-3 dimers bind to specific DNA sequences known as interferon-stimulated response elements (ISREs) present in the promoters of target genes, inducing type I interferon production (IFN-α and IFN-β) [118]. Moreover, in response to TLR-3 activation by BRSV, γδ T cells present higher levels of monocyte chemoattractant protein-1 (MCP-1, also known as C-C motif chemokine ligand 2, CCL2) [119]. MCP-1 directs leukocyte infiltration, affects T cell proliferation and function, activates macrophages, and promotes inflammation. MCP-1 may also act as a regulator in the polarization of T cells toward a Th2 phenotype [120–122].

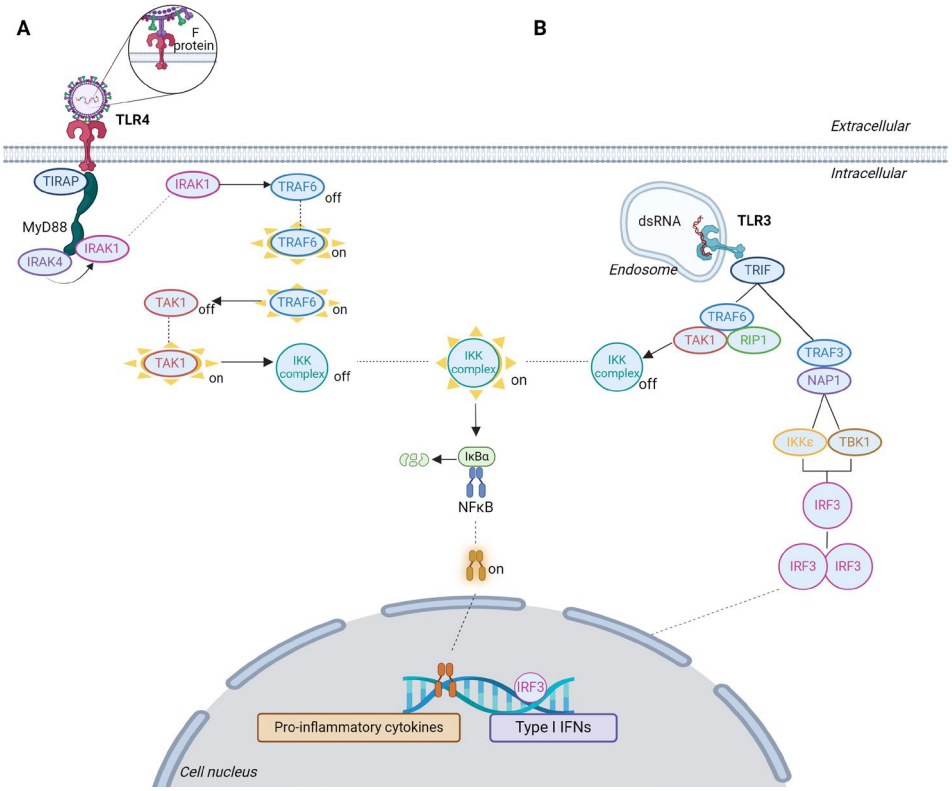

Figure 4. Schematic representation of an endosomal and a surface TLR signaling. **A)** Recognition of F by TLR-4 culminates in NFκB activation and translocation to the nucleus, initiating the secretion of pro-inflammatory cytokines. **B)** Recognition of dsRNA replication products by TLR-3 leads to the activation of both NFκB and IRF3 and transcription of type I IFN and pro-inflammatory cytokines. Abbreviations: BRSV= Bovine respiratory syncytial virus; dsRNA= double-stranded RNA; TLR-3 and TLR-4= Toll-like receptor 3 and 4; IκBα= nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; TRIF= Toll interleukin 1 receptor (TIR)-domain-containing adaptor protein inducing interferon-beta; TRAF3 and TRAF6= Tumor necrosis factor-alpha (TNF-α)-receptor-associated factor 3 and 6; NAP1= NFκB-activating kinase (NAK)-associated protein 1 (NAP1); Nuclear factor kappa B= NFκB; TBK1= TANK binding kinase 1 (TBK1); IRF3= interferon regulatory factor 3; TAK1= transforming growth factor beta (TGF-β)-activated kinase 1; RIP1= Receptor interacting protein 1; NFκB= Nuclear factor kappa B; IL-1 and 6= Interleukin 1 and 6; TNF-α= Tumor necrosis factor-alpha; F protein= Fusion protein; TIRAP= Toll/interleukin-1 receptor like-domain containing adaptor protein; MyD88= Myeloid differentiation primary-response 88; IRAK1 and 4= Interleukin 1 receptor (IL-1R)-associated kinase 1 and 4. Figure created with BioRender.com.

Infection with BRSV leads to increase of several cytokines and chemokines in the circulation including IL-6, TNF-α, IL-18, chemokine-x-c motif ligand (CXCL8), CCL2, CCL3, and CCL5, mediating the subsequent influx of leukocytes, predominantly neutrophils [123,124]. Whole blood transcriptome analysis in BRSV-infected dairy calves revealed that several genes in the Kyoto encyclopedia of genes and genomes (KEGG) pathway for Influenza A were influenced by the infection, including MHC genes (BOLA-DQ5, BOLA-DQ, MX1BOLA-DQB), chemokines and cytokines (CXCL8, IL-12B, CXCL10), viral detection (DDX58 and IFIH1, which encodes MDA5), cellular antiviral response and innate immune signaling (IRF7, EIF2AK2, RSAD2, OAS1Y, OAS1Z) [98,125].

Infected lungs show intense neutrophilic infiltration that coincides with the occurrence and peak of clinical signs [63,126]. NETosis is a specialized form of cell death in neutrophils characterized by the release of neutrophil extracellular traps (NETs). This process involves expulsing DNA, histones, and antimicrobial proteins from the neutrophil, forming a web-like structure that traps and neutralizes pathogens [127–129]. RSV stimulates NETosis through TLR-4, 7, and 8, resulting in the release of reactive oxygen species (ROS) [130–132]. The mechanisms underlying NETs formation require ROS production, and while both NETosis and ROS are important immune mechanisms, exacerbated responses are tissue damaging. ROS and NETosis have been implicated in lower respiratory tract disease pathogenesis caused by BRSV and RSV [133–135]. Bronchoalveolar lavage from BRSV-infected calves are also consistent with neutrophil activation and NETosis, and decreased antioxidant repairing mechanisms that would counter act tissue damage [134].

Oxidative stress, an imbalance in the production of ROS and antioxidant responses, was also reported *in vitro* in BRSV infection of bovine turbinate primary cell line and *in vivo* in lesion versus no-lesion lungs tissue of BRSV infected calves, with increased ROS genes and cyclooxygenase (COX)-2 (infected vs. non-infected), and decreased Myeloperoxidase (MPO), NADPH oxidase (NOX)1, NOX4, NOX5 and superoxide dismutase (SOD) (lesioned vs non-lesioned lung in infected animals) [136]. SOD-1 and SOD-2 products are anti-oxidative and mediate the removal of oxygen radicals. The evaluation of global changes in mRNA abundance in healthy lung and lung lesions from BRSV infected calves also pointed to oxidative stress and the production of nitric oxide and ROS to be activated in the tissues of the BRSV challenged animals on another study [137]. While nitric oxide and reactive oxygen are immune mechanisms involved in pathogen destruction and apoptosis, they have been shown to be used by viruses to facilitate replication [138]. Supporting the idea that the virus may benefit from the intense lung neutrophilic infiltration and their oxidative response, differential regulation of cytokine production by IL-17A and IL-17F (which supports neutrophils function), with downregulation of IL-10, IL-6, and CCL3, has also been reported in lung lesions [137]. Collectively, transcriptome analysis of lesion or non-lesion lung tissue from calves infected with BRSV supports dysregulated oxidative stress, cell damage, and depressed innate and adaptive immune functions in lung lesions [137,139]. Down-regulation of B and T cells activation and differentiation, cytokine production, and adaptive immune response were typical findings in lesioned tissue samples, while chemotaxis of immune cells (particularly innate immune cells) was increased. Differential gene expression suggested that depressed functional activity of innate immune cells in lesions and increased chemotaxis may be a compensatory effect in response to the shortage of function of these cells in resolving the infection.

Limiting inflammation and immune cells influx into the lung therapeutically by the use of broad-spectrum antioxidants and nonsteroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors, have been attempted to curb tissue damage and improve lung function and disease outcome [140–143]. While in mice, the use of such drugs was promising, in calves, ibuprofen (an NSAID) treatment of BRSV-infected calves reduced weight loss and clinical scores but led to increased viral titers [144], suggesting that COX-2 is involved in both viral clearance and immunopathology in calves. In contrast, the use of Ibuprofen as an adjunct therapy with antiviral fusion protein inhibitor (FPI) was shown

to enhance the specific antiviral effect of FPI and reduce the damaging impact of prostanoids and oxidative stress [62,139,145].

5.2. Adaptive immunity

BRSV may cause exacerbated respiratory tract inflammation and recruitment of innate leukocytes into the lungs of affected animals, accompanied by decreased cell function and tissue-sparing mechanisms [136,137,139,146]. Adaptive immunity initiates by the action of professional antigen presenting cells (APCs) that carry foreign material from the infection site into secondary lymphoid organs to activate T, while lymph drainage of infected sites carries native antigens for B cells recognition and activation. Innate defense events may impact the ability of dendritic cells to properly and timely activate protective adaptive responses. Besides, BRSV is most severe in young animals, which present inexperienced immune systems and a concomitant downregulation of several immune mechanisms [147]. Immunosuppression in neonates is highly dynamic and tightly regulated, with a short and early stage where T cell subsets synergize towards a narrow pro-tolerogenic window that favors non-inflammatory colonization [147]. BRSV infection in neonates may also occur during the pulmonary transition to life after birth. Significant physiological changes in respiratory and hemodynamic function are initiated by breathing at birth and clamping of the umbilical cord, and a complex adaptation takes place in several weeks after birth [148–150]. While those processes contribute to the maturation of the lungs and the immune system, they hamper effective immune responses against BRSV [151]. Additionally, BRSV employs different strategies to curb innate and adaptive immune responses, with detrimental effects on immunological memory, which is incomplete in both bovine and human hosts [5,152]. During infection, dendritic cell function may be subverted, leading to imbalanced adaptive immune responses, with more protective responses, T helper (Th) 1, being delayed or suppressed (low IL-12 production) and harmful responses (Th2, and with some evidence Th17) being favored (IL-4, IL-10, IL-33, IL-13, IL-22, IL-6, TGF-β).

T cells are important effector immune cells but only become activated after a highly orchestrated program of differentiation. On initial encounter with dendritic cells (DC) in secondary lymphoid organs, naïve T cells integrate signals through their T cell receptor (TCR) and through co-stimulatory molecules interactions [153]. This initial "priming" stimulation is amplified by paracrine cytokine signaling from the APC, which dictates the function of T cells upon activation. For example, IL-12 differentiates CD4 T cells into Th1 phenotype [154–156], IL-12 and type I IFN activate naïve CD8 T cells into cytotoxic CD8 T cells [157]. IL-4 secretion differentiates CD4 T cells into their Th2 phenotype, while IL-6 and TGF-β production together leads to Th17 differentiation. Additionally, paracrine and autocrine IL-2 signaling allows T cells to initiate a program of rapid and extensive division and differentiation [158,159].

The development of an adaptive immune response, especially Th1 responses, is associated with BRSV infection control, and clearance of BRSV is concomitant with the induction of BRSV-specific CD8 T cell responses in peripheral blood and their influx into the lungs [160–164]. In cattle, depletion of CD8 T cells results in delayed clearance of BRSV from calves' upper and lower respiratory tract and more severe pulmonary pathology [161,165–167]. Bronchial lymph node transcriptome analysis in BRSV-infected calves revealed intense activation of host immune response genes, with granzyme B being the most upregulated gene in the lymph node of calves in two separate studies [90,168]. Granzyme B is a serine protease found in natural killer (NK) cells and cytotoxic T cell granules, secreted with perforin to induce apoptosis in target cells, mediating cytotoxicity and viral control [169] and limiting inflammation [170]. Granzyme has also been shown to be increased in CD8 T cells, NK cells and in CD4 T cells in tracheal aspirates from children infected with RSV [171]. Similar to whole blood transcriptome analysis, the KEGG pathway for Influenza A was enriched, and upregulated genes included cytokines responsible for the induction of the febrile response, programmed cell death, and interferon-stimulated genes [90]; finding also supported by Tizioto et al. [168]. No

indication of Th2 polarization was observed, although genes related to B cell receptor signaling were consistently enriched. Likewise, IL-12, involved in Th1 polarization, was not detected as a differentially expressed gene, even though acute phase response signaling was upregulated [90,168]. Nevertheless, it is worth noting that calves in these studies presented mild to subclinical infections, and sampling was obtained at a single time point (day 7 post-infection).

Features of severe BRSV infection in calves include rapid neutrophil infiltration, excessive mucus production, delayed virus-adaptive T cell response [126,172], and expression of Th2 or Th17 cytokines, such as IL-4, IL-13, and IL-17 [173–180]. Therapeutic inhibition of IL-17 by digoxin can limit BRSV-associated disease in neonatal calves without significant adverse impacts on the viral burden [173]. Regarding recognition of BRSV proteins, T cell responses are directed at epitopes within several viral proteins, including the N, M, NS2, M2-1, F, and G [181]. The F and G proteins are major antigenic CD4 T cell targets in humans and cattle [172,182,183]. The F protein of RSV and BRSV is the most thoroughly studied of these viruses and is described to contain multiple antigenic regions [69,184,185].

Mucosal immunity is also important in protection against BRSV to limit virus replication at the initial site of infection [69,186,187]. Studies in calves in which the primary mucosal response to BRSV was inhibited by maternally acquired antibodies (MDA) and studies of BRSV vaccine efficacy suggest that the ability to mount a rapid secondary mucosal Immunoglobulin (Ig) A response may be more important in protection than the level of pre-existing mucosal antibodies [69,146,188–190]. There is also evidence that while the presence of MDA leads to poor antibody response to vaccination, memory cell formation is preserved, and vaccines may still elicit protectful responses to subsequent challenges with rapid antibody production and T cell responses, specific IgG, and neutralizing antibodies [191].

The persistence of memory T cells post-infection ensures a more rapid and efficient response upon re-exposure to the virus, although BRSV usually leads to suboptimal memory responses [69]. Despite the multiple protective mechanisms, cattle, similar to RSV in humans, still experience multiple BRSV reinfections. Subsequent infections tend to be less severe but maintain the virus circulation in the population, contributing to the infection of highly susceptible young calves.

While adaptive immunity is essential for viral clearance, these responses are delayed by the many evasion molecules employed by the virus, the physiological immune regulation in neonatal calves, and the inexperienced immune system of young calves. Likewise, antibodies and T cells have also been shown to contribute to the BRSV pathogenesis and may participate in pathology, especially Th2 cells that support the production of BRSV-specific IgE antibodies and eosinophil involvement in the context of formalin-inactivated vaccines [160].

6. Viral immune evading mechanisms

BRSV has evolved several mechanisms for evading the immune response to facilitate prolonged virus replication in the host. The two nonstructural proteins, NS1 and NS2, are the first to be produced and, therefore, abundant in early infection [192]. Recombinant BRSV lacking NS1/NS2 proteins induced greater type I IFN levels in bovine cell cultures when compared to wild-type BRSV, and the viral replication was significantly higher in 2-year-old calves challenged with wild-type BRSV than in those that received the recombinant BRSV lacking NS proteins [193]. Besides, NS1 and NS2 can work independently and together to suppress IFN production [194,195]. NS1 binds to MAVS, .the adaptor protein that the RIG-I receptor uses in the signaling pathway, and NS2 interacts with the CARD domain of RIG-I. These interventions inhibit IRF3 activation, preventing the downstream signaling (Fig. 5A and B) [196–198]. Interference by NS proteins in the IRF3 pathwayhas been described to both RSV and BRSV [195,199]. Additionally, the G protein from RSV was shown to inhibit IFN-stimulated genes (ISGs) in epithelial cells from mice [201] and humans [202].

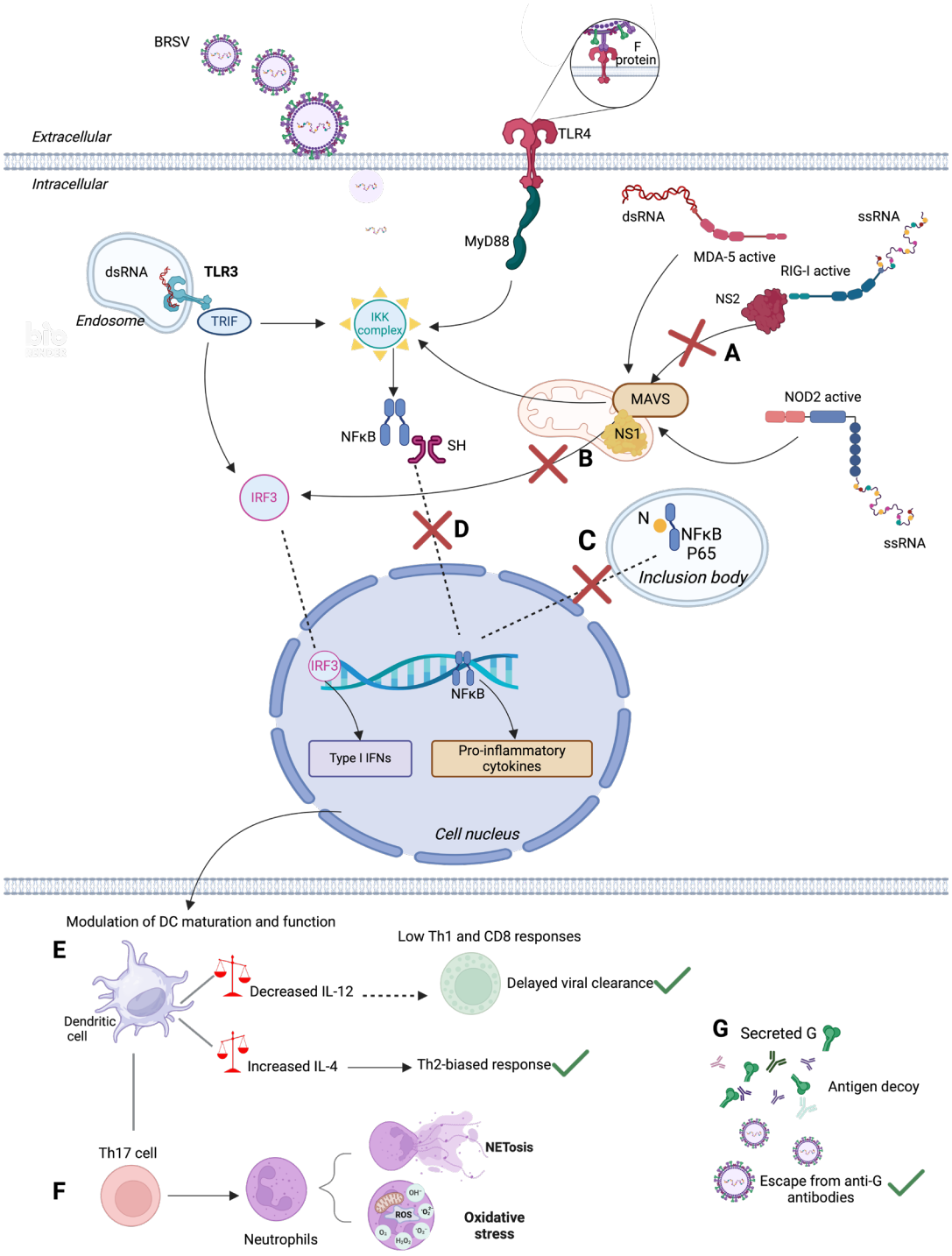

Figure 5. Schematic representation of some of the Respiratory Syncytial Virus immune evading mechanisms. A) NS2 interacts with the CARD domain of RIG-I; **B)** NS1 binds to MAVS, the adaptor protein used by the RIG-I receptor on the signaling pathway. These interventions inhibit IRF3 activation, preventing the downstream pathway events and hindering type I IFN production. **C**) N protein is involved in sequestering the P65 subunit of NFκB into intracytoplasmic inclusions bodies, leading to decreased translocation to the nucleus; **D)** The SH protein interferes with pro-inflammatory cytokines production through the NFκB pathway. **E)** Interference with IRF-3 and NFκB pathways modulate the function of dendritic cells and may suppresses their maturation resulting in decreased IL-12, which is essential for CD8 T cell differentiation and viral clearance, and increased IL-4, leading to poorly protective and potentially detrimental Th2-biased responses. **F)** BRSV infection may induce Th17 differentiation, contributing to neutrophil accumulation, NETosis, and oxidative stress, which are thought to enhance pathology. **G)** BRSV secreted G protein (sG) acts as a decoy antigen, sequestering antibodies away from the actual virion. Abbreviations: BRSV=

Bovine respiratory syncytial virus; dsRNA= double-stranded RNA; ssRNA= single-stranded RNA; TLR-3 and TLR-4= Toll-like receptor 3 and 4; TRIF= Toll interleukin 1 receptor (TIR)-domain-containing adaptor protein inducing Interferon-beta; IRF3= Interferon regulatory factor 3; NFκB= Nuclear factor kappa B; IL-4, 6, 8, 12 and 17= Interleukin 4, 6, 8, 12 and 17; CCL5= Chemokine ligand 5; TNF-α= Tumor necrosis factor-alpha; F protein= Fusion protein; SH= Small hydrophobic protein; NS1 and 2= Nonstructural proteins 1 and 2; G= Major attachment glycoprotein; N= Nucleocapsid protein; P= Phosphoprotein; MyD88= Myeloid differentiation primary-response 88; MAVS= Mitochondrial antiviral-signaling protein; RIG-I= Retinoic acid-inducible gene I; NOD2= Nucleotide oligomerization domain 2. Figure created with BioRender.com.

Inclusion bodies are highly ordered structures performing multiple roles in the virus life cycle, including the compartmentalization of virus replication and transcription (Fig. 2A). Recently, BRSV inclusion bodies were shown to participate in evasion mechnisms by sequestratering cellular proteins involved in the antiviral response. In BRSV infected cells, NFκB component p65 is recruited to inclusion bodies during viral replication (Fig. 5C), blocking NFκB translocation to the nucleus and transactivation of NFκB reporter, even after tumor TNF-α stimulation. While inclusion bodies were shown to contain BRSV N, P, L, M and M2-1 proteins, light electron microscopy indicated colocalization, pointing to a possible interaction, between N and p65 in BRSV inclusion bodies [220]. The SH protein was also shown to prevent infected cells from apoptosis *in vitro* and to interfere with pro-inflammatory cytokine production through the NFκB pathway inhibition (Fig. 5D) [203,204].

By interfering with antiviral mechnisms, BRSV infection also suppress the maturation of dendritic cells as the production of IL-6, IL-8, regulated upon activation normal T cell expressed and presumably secreted (RANTES, also known as chemokine ligand 5, or CCL5) and TNF-α expression is downregulated, which can all be at least partially, a result of type I IFN inhibition (Fig. 5E) [200]. The interference on the type I IFN pathway is so significant that type III IFN may predominate in RSV antiviral responses, differing from most other viruses [95]. Cytotoxic T cells and Th1 cells become activated by the IL-12 secreted by dendritic cells [205]. However, modulation of DC activitity by BRSV inhibits IL-12 secretion, and may favor the release of interleukin-4 (IL-4). Lack of IL-12 and the presence of IL-4 results in a Th2-biased response (Fig. 5E) [206]. Other studies have shown that human RSV interaction with dendritic cells reduces their ability to produce essential cytokines that would lead to an effective T cell response [66], and further research with BRSV described the same in experimentally infected calves [207]. In this scenario, protective BRSV-specific CD8 T cells responses are suppressed or delayed [66,208]. This Th2-biased response, induced not by NS proteins alone, is correlated with disease severity, as the clinical signs are not necessarily caused by the virus alone but also by the immune response to the infection.

The N protein can also inhibit T cell activation in RSV infection [209]. The NS1 was shown to reduce IL-17 production [210], shown to decreased viral load in mice lungs [211]. However, Long et al. [212] reported an association between increased IL-17 levels and RSV-caused pneumonia severity in mice. BRSV-infected calves also express significant levels of IL-17 (primarily produced by activated γδ and Th17 cells) [175,213]. *In vitro* analyses also showed high IL-17 production after BRSV infection and even higher when the peripheral blood mononuclear cells (PBMC) were co-infected with Mannheimia haemolytica [175]. In neonatal BRSV-infected calves, reduced IL-17 levels lead to improved disease outcomes and milder disease. Nevertheless, BRSV infection was shown to lead to Th17 cell differentiation [175]. The consequent IL-17 production recruits neutrophils [214], leading to NETosis and ROS formation enhancing pathology (Fig. 5F) [130].

Besides being produced in its full length as transmembrane protein, RSV G sequence contains a second translation initiative site that leads to the production of truncated G form, that is secreted (sG), which is preserved in RSV and BRSV viruses and has been suggested as an evading mechanism(Fig. 5G) [215]. In addition, the G protein participates in the Th2-biased induced response, as it enhances IL-4 levels, which leads to Th2 production and suppresses the Th1 transcription factor [216]. The F protein F, despite

acting mainly to incite immune response and not to evade it, can be a cause of damage to the host, as the F-TLR-4 signaling pathway induces the formation of NETs [217]. NETs have been shown to provoke extensive injury to the respiratory tract during viral infections. However, *in vivo*, the formation of NETs under BRSV infection has not been evaluated so far. With all this put together, BRSV has the potential to evade the host immune defenses and succeed in further replication and spreading, emphasizing the need for greater vaccines against this agent.

In summary, the many viral proteins play a role in delaying the translation of viral detection into effective immune responses. The inhibition of type I IFN and of the establishment of an anti-viral state paradoxically occurs with the abundant recruitment of phagocytes that poorly control viral replication and spread. The resulting adaptive response, in the context of decreased Th1 polarizing cytokines, may result in Th2 or Th17 biased responses, which further allow for viral replication, phagocyte recruitment, and inflammation, aggravating the clinical disease. Likewise, the virus may benefit from the induction of poorly protective and sometimes harmful adaptive immune responses, in detriment of cytotoxic T cell and supporting Th1 responses that would halt viral replication and control inflammation.

7. Conclusion

BRSV shares many characteristics to its human homologous, RSV [218,219]. For instance, BRSV clinical signs are the most severe in younger and immunocompromised calves [16]. However, the RSV and BRSV may present different features and challenges. While the literature is increasingly incorporating BRSV studies, there is still a relative lack of studies focused on BRSV. The present study described the main PRRs involved in the anti-BRSV response, which MAMP they recognize, and the further signaling pathway initiated by viral recognition. Additionally, this paper presents the scaping mechanisms developed by this virus that may contribute to severe disease.

Funding:

This research was funded by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brazil - Finance Code 001. This work was supported by intra-mural departmental funds from Oklahoma State University, College of Veterinary Medicine.

Author contribution: LSB, MIF, and NYB contributed to writing the manuscript. AKF, GF, and MFM: writing and editing the manuscript. AKF was responsible for providing the histological images. LSB and MFM produced the fluorescence images. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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2.2 Artigo 2

Identification of nucleolin as a potential cellular receptor for Bovine Respiratory Syncytial Virus

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Será submetido à revista Veterinary Immunology and Immunopathology

Identification of nucleolin as a potential cellular receptor for Bovine Respiratory Syncytial Virus

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Abstract

Bovine Respiratory Syncytial Virus (BRSV) is an important pathogen of acute respiratory disease in cattle and is a key contributor to the bovine respiratory disease complex (BRD), posing a significant threat to livestock production worldwide. Despite its relevance, many features regarding the BRSV infection remain incompletely characterized, including the host factors mediating the initial steps of infection. In this study, we examined the role of nucleolin (NCL) during BRSV entry in primary bovine cells. NCL is a key protein involved in many cellular activities and that acts as a cell receptor for various agents. We evaluated how BRSV infection modulates cellular NCL expression and localization. Additionally, we evaluated how blocking NCL by neutralization or specific aptamers impacted BRSV infection of primary host cells. Immunofluorescence indicates BRSV infection leads to transiently increased NCL expression and to its translocation to cytosol and perinuclear spaces. The functional inhibition of NCL using either a specific antibody or the AS1411 aptamer resulted in a significant reduction in viral infection in permissive cells ($p<0.0001$), with a depletion of more than 80% up to almost 100%, respectively. Taken together, these data suggest that NCL is involved in BRSV infection. Our findings expand the current understanding of the interactions between BRSV and its host, by identifying NCL as a potential cellular component involved in the early steps of BRSV infection in bovine cells.

Keywords: BRSV, cell receptor, immunofluorescence, functional blockage, nucleolin.

1. Introduction

Bovine Respiratory Syncytial Virus (BRSV) is responsible for primary acute respiratory disease in cattle, and it's also associated with the bovine respiratory disease complex (BRD), with clinical signs ranging from mild nasal discharge and coughing to dyspnea and severe pneumonia (1,2). First identified in the 1970s in Europe (3), it was quickly reported worldwide (4,5), resulting in a substantial economic burden to the livestock industry globally (6). Also known as *Orthopneumovirus bovis*, BRSV belongs to the *Mononegavirales* order (7), which comprises non-segmented single-stranded negative-sense RNA (ssRNA-) viruses. Within this order, BRSV is classified in the

Orthopneumovirus genus, along with its human counterpart, Respiratory Syncytial Virus (RSV). Orthopneumoviruses' genome is composed of 10 genes encoding 11 proteins (NS1, NS2, N, P, M, SH, G, F, M2.1, M2.2, L). Besides genomic similarity, BRSV and RSV share many pathogenesis and epidemiology features, but also present unique aspects, such as their specific host ranges (8).

While the RSV contains a major attachment glycoprotein (G), its F protein was shown to be sufficient to provide attachment and viral entry *in vitro* (9,10). A number of host proteins have been shown to mediate RSV viral entry, functioning as either cellular receptor or co-receptors to the virus. Among these receptors, c-type lectins, CX3C chemokine receptor 1 (CX3CR1), and heparan sulfate proteoglycans (HSPGs) have been shown to play a role on RSV entry, most likely increasing infectivity by enhancing adhesion through strong interaction with RSV G protein and weak interactions with F protein, and by mediating cell-to-cell spread. Strong evidence indicates that nucleolin (NCL) interaction with F is the most relevant step for viral fusion and entry (11), with insulin-like growth factor-1 receptor (IGF1R) being an important co-receptor leading to the recruitment of NCL to the cell surface (12). However, there is a paucity of studies evaluating BRSV in bovine cells (13).

NCL is a highly conserved phosphoprotein involved in many cellular activities including stability, transport, and translation of ribosomal RNA, and microtubule anchoring in interphase cells (14–17). On the cell surface, NCL acts as a receptor for a variety of cytokines, growth factors and matrix proteins, also acting as a scavenger receptor (18–23). This protein has also been shown to mediate the entry of numerous other ssRNA viruses, including Enterovirus 71 (EV71) (24), Rabbit hemorrhagic disease virus (RHDV) (25), and Human parainfluenza virus type 3 (HPIV-3) (26); as well as certain bacteria and toxins (19). Besides the surface receptor activity, nucleolin is involved in a wide range of cellular activities, modulating both proliferation and survival (27). The composition and structure of NCL provides the ability for shuttling between cellular compartments, and those features play an important role in the NCL's involvement in cancer (28). Here, we investigate the involvement of NCL in BRSV entry in primary bovine cells.

2. Material and Methods

2.1. Cells and viruses

Primary bovine turbinate cells (BT) were used to amplify the BRSV-GFP virus (Viratree) and the BRSV strain 375 (laboratory biorepository). Cells were grown in complete cell culture medium composed of minimal essential media (MEM) supplemented with 10% fetal bovine serum, l-glutamine (final concentration, 1.4mM), gentamycin (50mg/mL; IBI Scientific™), and 1% Antimycotic-Antibiotic 100× (Gibco™, Life Technologies) and maintained in humidified incubators at 37°C, with 5% CO_2. Virus titers were determined by limiting dilution at 5 days post-inoculation, using an Accu-Scope EXI-600 at 488 nm, and calculated by the Spearman–Karber method (29).

2.2. Cytotoxicity assay

Blocking antibodies and aptamers were evaluated for cytotoxicity using the MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) assay. BT cells were seeded into 96-well flat-bottom plate (FischerBrand - ThermoFischer Scientific™), at a density of $1x10^5$/mL, and incubated for 24 hours in a humidified incubator at 37°C with 5% CO_2. Antibodies (1 to 6µg/mL) and aptamers (5 to 20µM) were added and incubated for 1 hour. Cells were then washed and cultured for additional 72 hours. Untreated cells were used as a negative control. Production of the reduced MTT formazan by living cells was determined by spectrophotometry (540nm) (SpectraMax™ M2, Molecular Devices). Cell viability was calculated from the ratio of the absorbance of the sample wells and control wells and the concentration. Treatments yielding >90% viability were considered not cytotoxic.

2.3. Immunofluorescence assay

BT cells were seeded into 96-well flat-bottom plate (FischerBrand - ThermoFischer Scientific™) and maintained with supplemented MEM in a humidified incubator at 37°C, with 5% CO_2, for 24 hours. The cells were infected with BRSV strain 375, MOI of 3. Uninfected cells were used as a negative control. The viral inoculum was removed, and cells were fixed with 4% paraformaldehyde at different time-points, being: 0, 10, 30, and 45 minutes post-infection. Following, the wells were permeabilized with 0.2% Triton X-

100, washed, and incubated with 1% Bovine Serum Albumin (BSA) to block nonspecific antibody binding. Following the incubation with BSA, the primary antibodies were applied. For the nucleolin staining: rabbit anti-nucleolin polyclonal IgG (Bethyl Laboratories™; 200µg/mL), goat IgG anti-rabbit biotin-conjugated (Merck™, Sigma-Aldrich), and streptavidin (Merck™, Sigma-Aldrich). Staining for the F protein of BRSV was performed using mouse anti-RSV F protein monoclonal IgG2b, shown to cross-react with BRSV F protein (Invitrogen™; 1mg/mL) and anti-mouse IgG2b Alexa Fluor™ 488 (Biolegend; 0.5mg/mL). Each antibody was diluted in 1% BSA immediately before use and incubated at room temperature (RT) for 1-2 hours. For nucleus staining, we used Hoechst 33342 (NucBlue™ Live ReadyProbes™ Reagent; Invitrogen), following the fabricant instructions. The reading was performed using a fluorescence microscope (Accu-scope model EXI-600) at wavelengths of 594nm, 488nm, and 380nm for nucleolin, F protein of BRSV, and nuclear staining, respectively. The images were merged with ImageJ software (https://imagej.net/ij/).

2.4. Blocking assays

BT cells were seeded at a density of $1x10^5$/mL in 96-well flat-bottom plates (FischerBrand - ThermoFischer Scientific™) and allowed to adhere overnight. The following day, cells were washed, and incubated for 1 hour in serum-free MEM containing either anti-nucleolin antibody (Bethyl Laboratories™, at concentrations of 1.0, 1.5, 2.0, 4.0, and 5.0µg/mL) or a NCL-targeting aptamer (AS1411, 5' GGTGGTGGTGGTTGTGGTGGTGGTGG 3', synthesized by IDT™) at concentrations of 2.5, 5.0, 10.0, and 20.0 µM. Controls wells treated with either an isotype control antibody (rabbit IgG, Southern Biotech™) or a non-targeting control aptamer (CRO, 5' CCTCCTCCTCCTTCTCCTCCTCCTCC 3'; IDT™). CRO is a cytosine-rich oligonucleotide used as a non-binding control due to its conformation (30). Before use, aptamers were folded (PBS 100mM Potassium Chloride) at 80°C for 10 minutes (SimpliAmp™, Applied Biosystems), followed by a slow cool down at room temperature for 1 hour. Following antibody or aptamer treatment, cells were washed to remove unbound ligands. BRSV-GFP at 0.01 MOI was added and unbound virus was removed

after 1 hour. Cells were cultivated in media at 37°C with 5% CO_2 for 24 hours before the infection was assessed.

2.5. Image acquisition and processing

Experiments were performed three independent times, and images were acquired 24 hours post-infection using Cytation 5 Cell Imaging Multimode Reader (BioTek, Agilen), on 40x magnification, under a 488nm blue laser (emission peak on green light, 509nm, suitable for GFP readings). The images were further analyzed through the ImageJ software (https://imagej.net/ij/), in order to obtain the mean fluorescence numbers on the green channel of all images.

2.6. Statistical analysis

Statistical analyses were performed using two-way Analysis of Variance (ANOVA) to assess the effects of specific anti-NCL antibody and aptamer on the susceptibility of permissive cells to BRSV infection. The two-way ANOVA was followed by a post-hoc test of Tukey's multiple comparisons. Analyses were conducted using GraphPad Prism (GraphPad Software, San Diego, CA, USA). A p-value of less than 0.05 was considered statistically significant, and the level of significance is presented in asterisks, as follows: * = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$, and **** = $p<0.0001$.

3. Results and discussion

To determine whether NCL participates in the early steps of BRSV infection, we first assessed whether viral inoculation altered the expression or subcellular distribution of nucleolin in primary bovine cells. We observed a modulation in NCL fluorescence during BRSV infection (Figure 1).

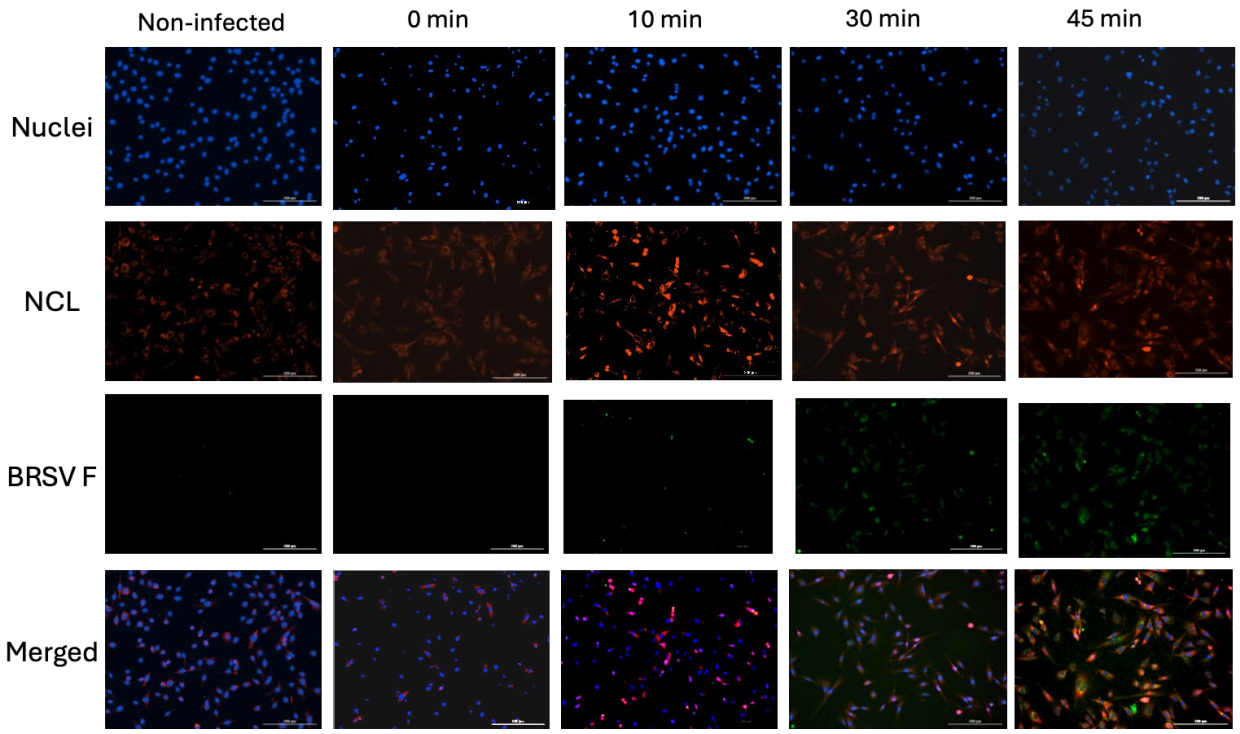

Figure 1. Nucleolin fluorescence signal modulation during BRSV infection. Primary bovine turbinate (BT) cells infected with BRSV s375 (MOI 3), fixated at time-points 0, 10, 30, and 45 minutes post-infection, stained for nuclei (blue), nucleolin (red), and BRSV's F protein (green). Final row: overlay of the three.

Our data suggests that surface NCL may be rapidly engaged during the first entry events, consistent with the infection dynamics described for RSV by Huong et al. (31). BRSV enters cells primarily through clathrin-mediated endocytosis (13), a common entry strategy among enveloped viruses and that has also been described for RSV. The transient recruitment of NCL observed after infection supports its involvement in receptor-mediated endocytic uptake during the initial entry stage.

Next, we evaluated if blocking of cellular NCL could interfere with BRSV infection in permissive primary bovine cells. For this, BT cells were incubated with specific anti-NCL antibody prior to viral challenge with a GFP-tagged BRSV, and images were obtained 24h post-infection (Figure 2A). The mean fluorescence values for each treatment were obtained through ImageJ software (Supplementary Table 1, Figure 2B). The values presented in the supplementary Table 2 indicate how much of the positive control

fluorescence was achieved with increasing doses of antibody (Figure 2C). There is a notable difference in fluorescent spots across the wells (Figure 2A), similarly to the results obtained by Tayyari et al. (11), in which human airway epithelial cells (1HAEo-) treated with anti-NCL antibody had significantly lower RSV infection rates, visible on fluorescence images of GFP-RSV. The inhibition of infection post treatment of the cells with antibodies directed against the potential receptor before viral infection is an essential criterion on functional receptor validation (Dimmock et al., 2007).

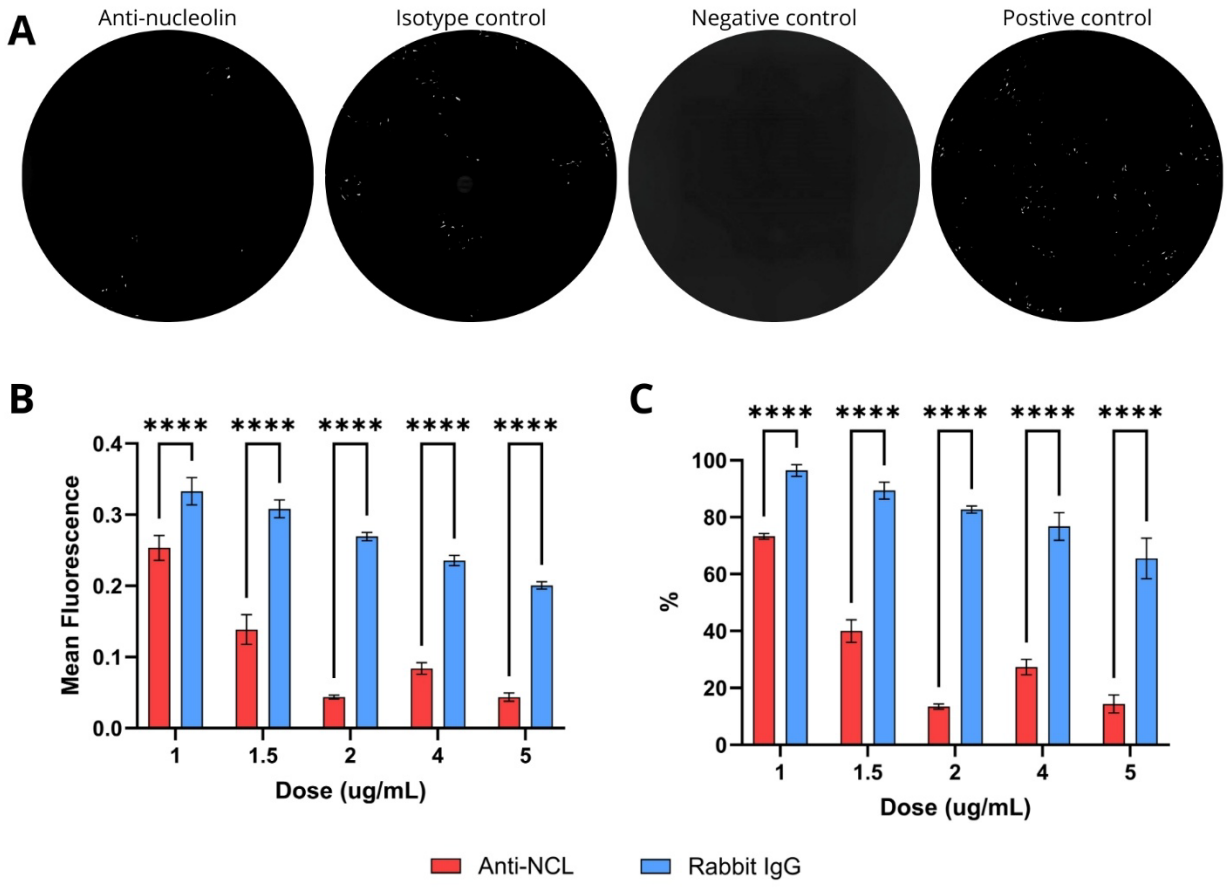

Figure 2. Treatment with antibody anti-nucleolin leads to notably reduced GFP-BRSV fluorescence 24h post infection. Primary bovine turbinate (BT) cells were treated with antibodies (anti-NCL and an isotype control) in a range from 1 to 5µg/mL, followed by infection with a GFP-tagged BRSV (MOI 0.01), and reading 24h post-infection. A: Representative images showing, from left to right: Anti-nucleolin: cells were treated with anti-NCL antibody (2µg/mL) prior to viral inoculation; Isotype control: cells were treated

with an isotype (rabbit IgG, 2μg/mL), prior to viral inoculation; Negative control: cells maintained untreated and not infected; Positive control: untreated cells, infected with GFP-BRSV. Images obtained on Cytation 5, 40x magnification, under 488nm excitation laser. The fluorescence images were converted to black and white for increased contrast, to facilitate visualization. B: collective data comparing GFP-BRSV mean fluorescence and C: relative mean fluorescence on wells treated with anti-NCL vs. isotype control at different doses (1 to 5μg/mL), 24h post-infection. Additionally, the values were normalized to the fluorescence intensity of the positive control (virus only), which was defined as 100%. The percentage of fluorescence for each sample was then calculated by dividing the sample's fluorescence intensity by the intensity of the positive control and multiplying by 100. The obtained values of mean and relative mean fluorescence were submitted to an ANOVA test, followed by Tukey's multiple comparisons. Asterisks indicate significance: ****$p<0.0001$.

This assay indicates a dose-dependent impact on BRSV infection caused by the pre-incubation of the cells with anti-NCL specific antibody, with almost 30% of reduction with a concentration as low as 1μg/mL, and a highly significant reduction of 86% with 2μg/mL ($p<0.0001$). The isotype control results indicate that the reduction on the BRSV infection rate achieved by the anti-NCL antibody treatment is specific. These results are comparable with the ones obtained by Tayyari et al. (11), in which the pre-treatment of human airway epithelial cells (1HAEo$^-$) with anti-nucleolin antibody (4μg) presented a remarkable nearly 100% reduction on RSV infection rate ($p<0.001$). In our experiment, a 4μg/mL dosage presented a blockage of 73%, that increased with 5μg/mL (85%), which presented a blockage statistically equal to 2μg/mL. That result is particularly interesting because even though the blockage increases with higher dosages, it achieved a limit, from which the infection reduction did not increase with growing antibody concentration. This observation might be explained by the consumption parameter (the ratio of receptor internalization to dissociation), originally described by Shankaran et al. (33) and further confirmed in the context of monoclonal antibodies by Krippendorff et al. (34). Nevertheless, it is worth mentioning that our study was conducted *in vitro*, in a controlled liquid environment without an air-liquid interface, under conditions that differ from those used by Krippendorff et al. (34), who employed an integrated pharmacokinetic model. In

systems with a high consumption parameter, further increases in affinity or concentration do not necessarily translate into increased inhibition. Additionally, nucleolin itself presents a behavior that might limit the success of surface targeting for its blockage: post-internalization, and with continuous stimuli, nucleolin is renewed on the cell surface, and with the pre-incubation with antibody happening once and not being re-applied, there may be a limit on maximal inhibition that can be achieved through surface targeting under the conditions applied on the experiment (35).

Dysregulated production of NCL is a marker of cancer and associated with worse prognosis (36). The participation of NCL on carcinogenesis and metastasis brought to light the potential of targeting nucleolin as a possible novel strategy on cancer therapy (37). In this scenario, accumulating data shows promising results of the application of the G-quadruplex aptamer AS1411, that specifically blocks nucleolin, in many types of cancer (38–42). Aptamers are small and non-immunogenic short nucleotide sequences, that can easily enter the cells and bind with high affinity to their targets. AS1411 was discovered by chance in the early 00's (43) and is now one of the most studied aptamers, used as an anti-nucleolin drug (39,44).

Therefore, to assess the hypothesis that NCL blockage through aptamer use has an effect on BRSV infection, we applied increasing concentrations of AS1411 prior to challenge with GFP-BRSV (Figure 3). The results suggest that aptamer-induced blockage of NCL significantly impacts BRSV susceptibility on primary bovine cells (Figure 3B). The GFP-fluorescence is visually impacted (Figure 3A) when cells were incubated with AS1411, ranging from 73.8 up to 99% ($p<0.0001$) reduced fluorescence at 2.5 and 20μM, respectively (Figure 3C and supplementary tables 3 and 4).

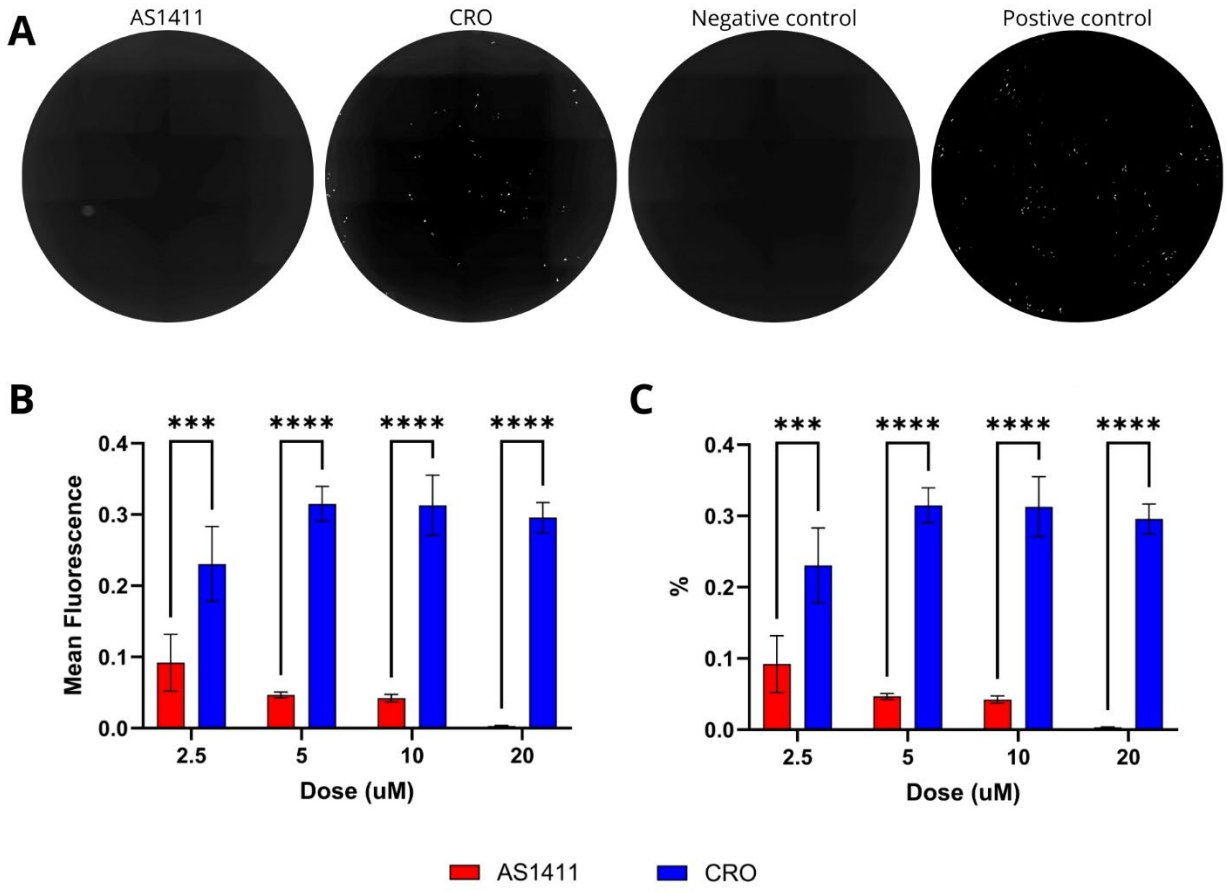

Figure 3. Treatment with nucleolin-specific AS1411 aptamer led to remarkably reduced GFP-BRSV fluorescence 24h post infection. Primary bovine turbinate (BT) cells were treated with the aptamers AS1411 and CRO in a concentration range from 2.5 to 20μM, followed by infection with a GFP-tagged BRSV (MOI 0.01), and reading 24h post-infection. A: Representative images showing, from left to right: AS1411: cells were treated with anti-NCL aptamer (20μM) prior to viral inoculation; CRO: cells were treated with the control aptamer (20μM), prior to viral inoculation; Negative control: cells maintained untreated and not infected; Positive control: untreated cells, infected with GFP-BRSV. Images obtained on Cytation 5, 40x magnification, under 488nm excitation laser. The fluorescence images were converted to black and white for increased contrast, to facilitate visualization. B: collective data comparing GFP-BRSV mean fluorescence and C: relative mean fluorescence on wells treated with AS1411 vs. CRO at different concentrations (2.5 to 20μM), 24h post-infection. The mean fluorescence values for each treatment were

obtained through ImageJ software. Additionally, the values were normalized to the fluorescence intensity of the positive control (virus only), which was defined as 100%. The percentage of fluorescence for each sample was then calculated by dividing the sample's fluorescence intensity by the intensity of the positive control and multiplying by 100. The obtained values of mean and relative mean fluorescence were submitted to ANOVA, followed by Tukey's multiple comparisons test. Asterisks indicate significance: ***$p<0.001$, ****$p<0.0001$.

The use of aptamer is strategically interesting because the treatment can continuously block NCL even before it is expressed on the cell surface, contrasting with the surface-targeting obtained with antibody treatments, which binds to NCL on the cell surface (45). In contrast, AS1411 can bind to NCL independent of its localization within the cell, which could explain the higher reduction in infection using AS1411 in comparison to the anti-NCL antibody, given the possible interference in NCL even before it translocates to the cell surface (46). Additionally, the half-life of the protein itself might affect the blocking capability, as the surface-expressed NCL has a short half-life of less than one hour, in contrast to the intracellular NCL, that can last for longer than eight hours (47).

The remarkable reduction on BRSV-infected cells with the application of the NCL-specific aptamer AS1411 corroborates with the hypothesis that NCL is involved in the BRSV viral pathogenesis ($p<0.0001$).

4. Conclusion

Taken together, our findings demonstrate that nucleolin plays an active role in the early stages of BRSV infection. The rapid increase and subsequent return to baseline levels of NCL signal post- inoculation suggests that it is dynamically engaged during the initial entry process. Functional inhibition of NCL through a specific antibody or the AS1411 aptamer significantly reduced viral infection in permissive cells, indicating nucleolin's involvement in BRSV infection in bovine cells. Overall, these results point to NCL as a relevant factor, contributing to the understanding of BRSV's interaction with its host, especially at early stages of the infection.

Supplementary

Supplementary tables

Table 1. Mean Fluorescence obtained in three independent rounds, the average, standard deviation, and standard error obtained for each dose of the antibody treatments (anti-nucleolin, and isotype control) and infected only conditions (positive control).

Treatment	Dose (µg/mL)	Mean Fluorescence 1	Mean Fluorescence 2	Mean Fluorescence 3	Average	Standard Deviation	Standard Error
Anti-Nucleolin	1.0	0.236	0.253	0.271	0.253	0.018	0.010
	1.5	0.115	0.147	0.154	0.139	0.021	0.012
	2.0	0.044	0.042	0.047	0.044	0.003	0.001
	4.0	0.093	0.077	0.082	0.084	0.008	0.005
	5.0	0.042	0.039	0.050	0.044	0.006	0.003
Rabbit IgG	1.0	0.319	0.325	0.355	0.333	0.019	0.011
	1.5	0.297	0.306	0.322	0.308	0.013	0.007
	2.0	0.274	0.271	0.263	0.269	0.006	0.003
	4.0	0.243	0.235	0.229	0.236	0.007	0.004
	5.0	0.202	0.195	0.205	0.201	0.005	0.003
Positive control	0	0.327	0.328	0.326	0.327	0.001	0.001

Table 2. Fluorescence relative to the positive control (100%), the average, standard deviation, and standard error obtained for each dose of the antibody treatments (anti-nucleolin, and isotype control).

Treatment	Dose (µg/mL)	Relative % 1	Relative % 2	Relative % 3	Average	Standard Deviation	Standard Error
Anti-Nucleolin	1.0	73.065	74.412	72.460	73.312	0.999	0.577
	1.5	35.604	43.235	41.176	40.005	3.948	2.280
	2.0	13.336	12.610	14.418	13.455	0.910	0.525
	4.0	28.182	24.329	29.496	27.336	2.686	1.551
	5.0	12.727	12.322	17.986	14.345	3.159	1.824
Rabbit IgG	1.0	98.762	95.588	94.920	96.423	2.053	1.185
	1.5	91.950	90.000	86.096	89.349	2.981	1.721
	2.0	83.897	82.763	81.401	82.687	1.250	0.722
	4.0	73.636	74.250	82.374	76.753	4.877	2.816
	5.0	61.212	61.611	73.741	65.522	7.121	4.111

Table 3. Mean Fluorescence obtained in three independent rounds, the average, standard deviation, and standard error obtained for each aptamer concentration (AS1411 and CRO).

Treatment	[ ] (µM)	Mean Fluorescence 1	Mean Fluorescence 2	Mean Fluorescence 3	Average	Standard Deviation	Standard Error
AS1411	2.5	0.113	0.117	0.046	0.092	0.040	0.023
	5.0	0.050	0.042	0.048	0.047	0.004	0.002
	10.0	0.041	0.038	0.048	0.042	0.005	0.003
	20.0	0.003	0.004	0.002	0.003	0.001	0.001
CRO	2.5	0.207	0.194	0.291	0.231	0.053	0.030
	5.0	0.338	0.318	0.289	0.315	0.025	0.014
	10.0	0.344	0.330	0.265	0.313	0.042	0.024
	20.0	0.320	0.286	0.281	0.296	0.021	0.012
Positive control	0	0.368	0.333	0.360	0.354	0.019	0.011

Table 4. Fluorescence relative to the positive control (100%), the average, standard deviation, and standard error obtained for each aptamer concentration (AS1411 and CRO).

Treatment	[ ] (µM)	Relative % 1	Relative % 2	Relative % 3	Average	Standard Deviation	Standard Error
AS1411	2.5	30.665	35.135	12.760	26.187	11.841	6.836
	5.0	13.569	12.613	13.315	13.165	0.495	0.286
	10.0	11.126	11.411	9.431	10.656	1.070	0.618
	20.0	0.814	1.201	0.555	0.857	0.325	0.188
CRO	2.5	56.174	58.258	80.721	65.051	13.611	7.858
	5.0	91.723	95.495	80.166	89.128	7.987	4.611
	10.0	93.351	99.099	73.509	88.653	13.426	7.752
	20.0	86.839	85.886	77.947	83.557	4.882	2.818

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This research was funded by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brazil; Finance code 001.

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3 Considerações finais

A resposta imunológica contra vírus é alvo de inúmeros estudos ao redor do mundo, especialmente contra o RSV, responsável pelo adoecimento e alta taxa de mortalidade em crianças ainda hoje (Lozano et al., 2012; Mazur et al., 2021; Nair et al., 2010). Apesar da alta homologia com o RSV, a infecção pelo BRSV apresenta uma série de particularidades, especialmente no que tange a imunologia do hospedeiro. A literatura atual conta com algumas revisões focadas no vírus bovino, no entanto, peca no que diz respeito à imunologia do agente. O primeiro artigo da presente dissertação visa contribuir em pesquisas futuras, apresentando um compilado dos principais fatores ligados à resposta imune contra o BRSV. De mesmo modo, o segundo artigo objetiva iniciar análises mais profundas e descrever o papel da nucleolina como potencial receptor celular envolvido na infecção pelo vírus.

A realização deste trabalho em parceria do LABVIR com a Universidade Estadual de Oklahoma (OSU/EUA) representa um marco de internacionalização para o grupo. Além da consolidação dessa cooperação e da contribuição para a literatura atual, a realização da presente dissertação trouxe à pesquisadora amadurecimento científico, profissional e pessoal. É válido citar que parte das análises relacionadas ao segundo artigo estão ainda em desenvolvimento e, por essa razão, não estão aqui descritas.

O presente estudo, na forma do segundo artigo que lhe consta, apresenta o potencial da nucleolina como receptor celular envolvido na infecção por BRSV. A colocalização da NCL com a proteína de fusão do RSV foi um dos métodos utilizados na determinação da mesma como receptor celular ao vírus humano, e é um dos passos a serem realizados no futuro. Desse modo, os resultados aqui apresentados sugerem que a NCL seja utilizada pelo BRSV. Tal sugestão advém do impacto causado pelo bloqueio da NCL em células primárias respiratórias, após realização do experimento em três repetições independentes.

Espera-se, futuramente, aprofundar as análises relacionadas ao receptor celular do BRSV, utilizando outros métodos, tais como western blotting, transfecção utilizando plasmídeos e células de inseto. De mesmo modo, ampliar a gama de potenciais receptores celulares a esse vírus, de modo a elucidar os meios de infecção utilizados pelo agente. Dando continuidade à pesquisa aqui descrita, espera-se desvendar os fatores ainda desconhecidos acerca da infecção pelo BRSV e contribuir de modo assertivo no desenvolvimento de melhores métodos de prevenção contra a doença causada por ele.

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